PATENT
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION of:	Confirmation No. **5077**
Laurent F. A. HENNEQUIN et al.	
Application No.: **10/520,266**	Group Art Unit: **1624**
Filed: **January 6, 2005**	Examiner **TRUONG, Tamthom Ngo**
FOR: **QUINZOLINE DERIVATIVES FOR USE IN THE TREATMENT OF CANCER**	

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Date: **April 28, 2008**

Sir:

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Submitted herewith are copies of the certified priority documents as filed in the International Bureau in International Application No. PCT/GB2003/002874 (filed July 4, 2003) to which priority is claimed in the subject application, specifically, Great Britain Patent Application No. 0215825.1 (filed July 9, 2002) and Great Britain Patent Application No. 0312897.2 (filed June 5, 2003). It is respectfully requested that these be placed in the file of the subject US National Stage application.

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Respectfully Submitted,
Morgan Lewis & Bockius LLP

Date: **April 28, 2008** By: _____

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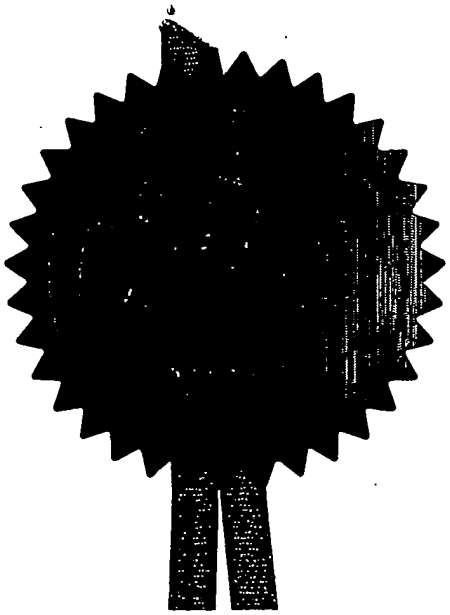

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1. Your reference — 100749

2. Patent application number
(The Patent Office will fill in this part) — 0215825.1 — 09 JUL 2002

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

AstraZeneca AB
S-151 85 Sodertalje
Sweden

Patents ADP number *(if you know it)* — 78224480003

If the applicant is a corporate body, give the country/state of its incorporation — Sweden

4. Title of the invention

QUINAZOLINE DERIVATIVES

5. Name of your agent *(if you have one)*

Tracey Bryant

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

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Mereside, Alderley Park
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Patents ADP number *(if you know it)* — 78224710002

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Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

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Signature Date

Authorised Signatory 8th July 2002

12. Name and daytime telephone number of person to contact in the United Kingdom

Jennifer C. Bennett - 01625 230148

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QUINAZOLINE DERIVATIVES

The invention concerns certain novel quinazoline derivatives, or pharmaceutically-acceptable salts thereof, which possess anti-tumour activity and are accordingly useful in methods of treatment of the human or animal body. The invention also concerns processes for the manufacture of said quinazoline derivatives, pharmaceutical compositions containing them and their use in therapeutic methods, for example in the manufacture of medicaments for use in the prevention or treatment of solid tumour disease in a warm-blooded animal such as man.

Many of the current treatment regimes for cell proliferation diseases such as psoriasis and cancer utilise compounds which inhibit DNA synthesis. Such compounds are toxic to cells generally but their toxic effect on rapidly dividing cells such as tumour cells can be beneficial. Alternative approaches to anti-tumour agents which act by mechanisms other than the inhibition of DNA synthesis have the potential to display enhanced selectivity of action.

In recent years it has been discovered that a cell may become cancerous by virtue of the transformation of a portion of its DNA into an oncogene *i.e.* a gene which, on activation, leads to the formation of malignant tumour cells (Bradshaw, Mutagenesis, 1986, 1, 91). Oncogenes give rise to the production of peptides which are receptors for growth factors. Activation of the growth factor receptor complex subsequently leads to an increase in cell proliferation. Oncogenes often encode abnormal versions of signal pathway components, such as receptor tyrosine kinases, serine-threonine kinases, or downstream signaling molecules such as the ras genes. The ras genes code for closely related small guanine nucleotide binding proteins which hydrolyse bound guanosine triphosphate (GTP) to guanosine diphosphate (GDP). Ras proteins are active in promoting cell growth and transformation when they are bound to GTP and inactive when they are bound to GDP. Transforming mutants of p21ras are defective in their GTPase activity and hence remain in the active GTP bound state. The ras oncogene is known to play an integral role in certain cancers and has been found to contribute to the formation of over 20% of all cases of human cancer.

When activated by ligand such as a growth factor, cell surface receptors which are coupled to the mitogenic response can initiate a chain of reactions which leads to the activation of guanine nucleotide exchange activity on ras proteins. When ras protein is in its active GTP-bound state, a number of other proteins interact directly with ras at the plasma membrane resulting in signal transmission through several distinct pathways. The best

characterised effector protein is the product of the raf proto-oncogene. The interaction of raf and ras is a key regulatory step in the control of cell proliferation. Ras-mediated activation of the raf serine-threonine kinase in turn activates the dual-specificity MEK (MEK1 and MEK2), which is the immediate upstream activator of mitogen activated protein kinase (MAPKs known as extracellular signal regulated protein kinases or ERK1 and ERK2). To date, no substrates of MEK other than MAPK have been identified, though recent reports indicate that MEK may also be activated by other upstream signal proteins such as MEKK1 and Cot/Tpl-2. Activated MAPK translocates and accumulates in the nucleus, where it can phosphorylate and activate transcription factors such as Elk-1 and Sap1a, leading to the enhanced expression of genes such as c-fos.

The ras-dependent raf-MEK-MAPK cascade is one of the key signalling pathways responsible for transmitting and amplifying mitogenic signals from cell surface to the nucleus resulting in changes in gene expression and cell fate. This ubiquitous pathway appears essential for normal cell proliferation and constitutive activation of this pathway is sufficient to induce cellular transformation. Transforming mutants of p21ras are constitutively active, resulting in raf, MEK and MAPK activity and cell transformation. Inhibition of MEK activity using either antisense raf, a dominant negative MEK mutant or the selective inhibitor PD098059 has been shown to block the growth and morphological transformation of ras-transformed fibroblasts.

The mechanism of activation of raf, MEK and MAPK is through phosphorylation on specific serine, threonine or tyrosine residues. Activated raf and other kinases phosphorylate MEK1 on S218 and S222 and MEK2 on S222 and S226. This results in MEK activation and subsequent phosphorylation and activation of ERK1 on T190 and Y192 and ERK2 on T183 and Y185 by the dual specificity MEKs. Whilst MEK can be activated by a number of protein kinases, and active MAPKs phosphorylate and activate a number of substrate proteins including transcription factors and other protein kinases, MEKs appear specific and sole activators of MAPKs and could act as a focal point for cross-cascade regulation. MEK1 and MEK2 isoforms show unusual specificity and also contain a proline-rich insert between catalytic subdomains IX and X which is not present in any of the other known MEK family members. These differences between MEK and other protein kinases, together with the known role of MEK (MEK 1, MEK 2) and, more recently MEK 5, in proliferative signalling suggest it may be possible to discover and employ selective MEK inhibitors as therapeutic agents for proliferative disease.

Accordingly, it has been recognised that an inhibitor of the MAPK kinase pathway should be of value as an anti-proliferative agent for use in the containment and/or treatment of solid tumour disease.

It is also known that several oncogenes encode tyrosine kinase enzymes and that certain growth factor receptors are also tyrosine kinase enzymes (Yarden *et al.*, Ann. Rev. Biochem., 1988, 57, 443; Larsen *et al.*, Ann. Reports in Med. Chem., 1989, Chpt. 13). The first group of tyrosine kinases to be identified arose from such viral oncogenes, for example $pp60^{v\text{-}Src}$ tyrosine kinase (otherwise known as v-Src), and the corresponding tyrosine kinases in normal cells, for example $pp60^{c\text{-}Src}$ tyrosine kinase (otherwise known as c-Src).

Receptor tyrosine kinases are important in the transmission of biochemical signals which initiate cell replication. Some of them are large enzymes which span the cell membrane and possess an extracellular binding domain for growth factors such as epidermal growth factor (EGF) and an intracellular portion which functions as a kinase to phosphorylate tyrosine amino acids in proteins and hence to influence cell proliferation. Various classes of receptor tyrosine kinases are known (Wilks, Advances in Cancer Research, 1993, 60, 43-73) based on families of growth factors which bind to different receptor tyrosine kinases. The classification includes Class I receptor tyrosine kinases comprising the EGF family of receptor tyrosine kinases such as the EGF, TGFα, Neu and erbB receptors, Class II receptor tyrosine kinases comprising the insulin family of receptor tyrosine kinases such as the insulin and IGFI receptors and insulin-related receptor (IRR) and Class III receptor tyrosine kinases comprising the platelet-derived growth factor (PDGF) family of receptor tyrosine kinases such as the PDGFα, PDGFβ and colony-stimulating factor 1 (CSF1) receptors.

It is also known that certain tyrosine kinases belong to the class of non-receptor tyrosine kinases which are located intracellularly and are involved in the transmission of biochemical signals such as those that influence tumour cell motility, dissemination and invasiveness and subsequently metastatic tumour growth (Ullrich *et al.*, Cell, 1990, 61, 203-212, Bolen *et al.*, FASEB J., 1992, 6, 3403-3409, Brickell *et al.*, Critical Reviews in Oncogenesis, 1992, 3, 401-406, Bohlen *et al.*, Oncogene, 1993, 8, 2025-2031, Courtneidge *et al.*, Semin. Cancer Biol., 1994, 5, 239-246, Lauffenburger *et al.*, Cell, 1996, 84, 359-369, Hanks *et al.*, BioEssays, 1996, 19, 137-145, Parsons *et al.*, Current Opinion in Cell Biology, 1997, 9, 187-192, Brown *et al.*, Biochimica et Biophysica Acta, 1996, 1287, 121-149 and Schlaepfer *et al.*, Progress in Biophysics and Molecular Biology, 1999, 71, 435-478). Various

classes of non-receptor tyrosine kinases are known including the Src family such as the Src, Lyn and Yes tyrosine kinases, the Abl family such as Abl and Arg and the Jak family such as Jak 1 and Tyk 2.

It is known that the Src family of non-receptor tyrosine kinases are highly regulated in normal cells and in the absence of extracellular stimuli are maintained in an inactive conformation. However, some Src family members, for example c-Src tyrosine kinase, are frequently significantly activated (when compared to normal cell levels) in common human cancers such as gastrointestinal cancer, for example colon, rectal and stomach cancer (Cartwright *et al.*, Proc. Natl. Acad. Sci. USA, 1990, 87, 558-562 and Mao *et al.*, Oncogene, 1997, 15, 3083-3090), and breast cancer (Muthuswamy *et al.*, Oncogene, 1995, 11, 1801-1810). The Src family of non-receptor tyrosine kinases has also been located in other common human cancers such as non-small cell lung cancers (NSCLCs) including adenocarcinomas and squamous cell cancer of the lung (Mazurenko *et al.*, European Journal of Cancer, 1992, 28, 372-7), bladder cancer (Fanning *et al.*, Cancer Research, 1992, 52, 1457-62), oesophageal cancer (Jankowski *et al.*, Gut, 1992, 33, 1033-8), cancer of the prostate, ovarian cancer (Wiener *et al.*, Clin. Cancer Research, 1999, 5, 2164-70) and pancreatic cancer (Lutz *et al.*, Biochem. and Biophys. Res. Comm., 1998, 243, 503-8). As further human tumour tissues are tested for the Src family of non-receptor tyrosine kinases it is expected that its widespread prevalence will be established.

It is further known that the predominant role of c-Src non-receptor tyrosine kinase is to regulate the assembly of focal adhesion complexes through interaction with a number of cytoplasmic proteins including, for example, focal adhesion kinase and paxillin. In addition c-Src is coupled to signalling pathways that regulate the actin cytoskeleton which facilitates cell motility. Likewise, important roles are played by the c-Src, c-Yes and c-Fyn non-receptor tyrosine kinases in integrin mediated signalling and in disrupting cadherin-dependent cell-cell junctions (Owens *et al.*, Molecular Biology of the Cell, 2000, 11, 51-64 and Klinghoffer *et al.*, EMBO Journal, 1999, 18, 2459-2471). Cellular motility is necessarily required for a localised tumour to progress through the stages of dissemination into the blood stream, invasion of other tissues and initiation of metastatic tumour growth. For example, colon tumour progression from localised to disseminated, invasive metastatic disease has been correlated with c-Src non-receptor tyrosine kinase activity (Brunton *et al.*, Oncogene, 1997, 14, 283-293, Fincham *et al.*, EMBO J. 1998, 17, 81-92 and Verbeek *et al.*, Exp. Cell Research, 1999, 248, 531-537).

Accordingly it has been recognised that an inhibitor of such non-receptor tyrosine kinases should be of value as a selective inhibitor of the motility of tumour cells and as a selective inhibitor of the dissemination and invasiveness of mammalian cancer cells leading to inhibition of metastatic tumour growth. In particular an inhibitor of such non-receptor tyrosine kinases should be of value as an anti-invasive agent for use in the containment and/or treatment of solid tumour disease.

We have now found that surprisingly certain quinazoline derivatives possess potent anti-tumour activity. It is believed that the compounds disclosed in the present invention provide an anti-tumour effect by way of inhibition of MEK enzymes that are involved in the MAPK kinase pathway and/or by way of inhibition of one or more of the non-receptor tyrosine-specific protein kinases that are involved in the signal transduction steps which lead to the invasiveness and migratory ability of metastasising tumour cells. In particular, it is believed that the compounds of the present invention provide an anti-tumour effect by inhibition of one or more of the MEK enzymes and/or by way of inhibition of the Src family of non-receptor tyrosine kinases, for example by inhibition of one or more of c-Src, c-Yes and c-Fyn. It is also known that c-Src non-receptor tyrosine kinase enzyme is involved in the control of osteoclast-driven bone resorption (Soriano *et al.*, Cell, 1991, 64, 693-702; Boyce *et al.*, J. Clin. Invest., 1992, 90, 1622-1627; Yoneda *et al.*, J. Clin. Invest., 1993, 91, 2791-2795 and Missbach *et al.*, Bone, 1999, 24 , 437-49). An inhibitor of c-Src non-receptor tyrosine kinase is therefore of value in the prevention and treatment of bone diseases such as osteoporosis, Paget's disease, metastatic disease in bone and tumour-induced hypercalcaemia.

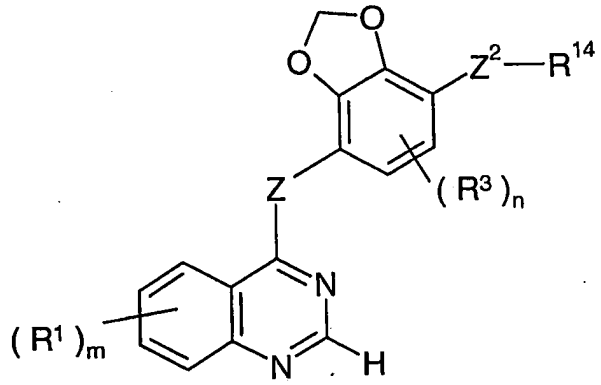
The compounds of the present invention are also useful in inhibiting the uncontrolled cellular proliferation which arises from various non-malignant diseases such as inflammatory diseases (for example rheumatoid arthritis and inflammatory bowel disease), fibrotic diseases (for example hepatic cirrhosis and lung fibrosis), glomerulonephritis, multiple sclerosis, psoriasis, hypersensitivity reactions of the skin, blood vessel diseases (for example atherosclerosis and restenosis), allergic asthma, insulin-dependent diabetes, diabetic retinopathy and diabetic nephropathy.

The compounds of the invention may possess inhibitory acitivity against the MEK enzymes that are involved in the MAPK kinase pathway. They may also possess an inhibitory activity against the Src family of non-receptor tyrosine kinases. Generally the compounds of the present invention may also possess potent inhibitory activity against the Src family of non-

receptor tyrosine kinases, for example by inhibition of c-Src and/or c-Yes, whilst possessing less potent inhibitory activity against other tyrosine kinase enzymes such as the receptor tyrosine kinases, for example EGF receptor tyrosine kinase and/or VEGF receptor tyrosine kinase.

It is stated in EP 837 063 that a range of 4-aminoquinazoline derivatives are useful in treating hyperproliferative diseases such as cancers. There is no disclosure therein of any 7-alkynyl-1,3-benzodioxol-4-yl-containing quinazolines or 7-alkenyl-1,3-benzodioxol-4-yl-containing quinazolines.

According to one aspect of the invention there is provided a quinazoline derivative of the Formula I



I

wherein **Z** is an O, S, SO, SO_2, $N(R^2)$ or $C(R^2)_2$ group, wherein each R^2 group, which may be the same or different, is hydrogen or (1-6C)alkyl;

m is 0, 1, 2, 3 or 4;

each R^1 group, which may be the same or different, is selected from halogeno, trifluoromethyl, cyano, isocyano, nitro, hydroxy, mercapto, amino, formyl, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, (3-6C)alkenoylamino, N-(1-6C)alkyl-(3-6C)alkenoylamino, (3-6C)alkynoylamino, N-(1-6C)alkyl-(3-6C)alkynoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino, N-(1-6C)alkyl-(1-6C)alkanesulphonylamino or from a group of the formula :

$$Q^1-X^1-$$

wherein X^1 is a direct bond or is selected from O, S, SO, SO_2, $N(R^4)$, CO, $CH(OR^4)$, $CON(R^4)$, $N(R^4)CO$, $SO_2N(R^4)$, $N(R^4)SO_2$, $OC(R^4)_2$, $SC(R^4)_2$ and $N(R^4)C(R^4)_2$, wherein R^4 is hydrogen or (1-6C)alkyl, and Q^1 is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl, or $(R^1)_m$ is (1-3C)alkylenedioxy,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, S, SO, SO_2, $N(R^5)$, CO, $CH(OR^5)$, $CON(R^5)$, $N(R^5)CO$, $SO_2N(R^5)$, $N(R^5)SO_2$, CH=CH and C≡C wherein R^5 is hydrogen or (1-6C)alkyl or, when the inserted group is $N(R^5)$, R^5 may also be (2-6C)alkanoyl,

and wherein any CH_2=CH- or HC≡C- group within a R^1 substituent optionally bears at the terminal CH_2= or HC≡ position a substituent selected from halogeno, carboxy, carbamoyl, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl or from a group of the formula :

$$Q^2-X^2-$$

wherein X^2 is a direct bond or is selected from CO and $N(R^6)CO$, wherein R^6 is hydrogen or (1-6C)alkyl, and Q^2 is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, cyano, amino, carboxy, carbamoyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino, N-(1-6C)alkyl-(1-6C)alkanesulphonylamino or from a group of the formula :

$$-X^3-Q^3$$

wherein X^3 is a direct bond or is selected from O, S, SO, SO_2, $N(R^7)$, CO, $CH(OR^7)$, $CON(R^7)$, $N(R^7)CO$, $SO_2N(R^7)$, $N(R^7)SO_2$, $C(R^7)_2O$, $C(R^7)_2S$ and $N(R^7)C(R^7)_2$, wherein R^7 is hydrogen or (1-6C)alkyl, and Q^3 is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl, (3-7C)cycloalkyl-

(1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any aryl, heteroaryl or heterocyclyl group within a substituent on R^1 optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino, N-(1-6C)alkyl-(1-6C)alkanesulphonylamino or from a group of the formula :

$$-X^4-R^8$$

wherein X^4 is a direct bond or is selected from O and $N(R^9)$, wherein R^9 is hydrogen or (1-6C)alkyl, and R^8 is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl, (1-6C)alkoxycarbonylamino-(1-6C)alkyl, or a group of the formula :

$$-X^5-Q^4$$

wherein X^5 is a direct bond or is selected from O, $N(R^{10})$ and CO, wherein R^{10} is hydrogen or (1-6C)alkyl, and Q^4 is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl and (1-6C)alkoxy,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo or thioxo substituents;

n is 0, 1 or 2; and

$\mathbf{R^3}$ is selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, (3-6C)alkanoylamino, N-(1-6C)alkyl-

(3-6C)alkenoylamino, (3-6C)alkynoylamino, N-(1-6C)alkyl-(3-6C)alkynoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino, N-(1-6C)alkyl-(1-6C)alkanesulphonylamino or from a group of the formula :

$$-X^6-R^{11}$$

wherein X^6 is a direct bond or is selected from O and $N(R^{12})$, wherein R^{12} is hydrogen or (1-6C)alkyl, and R^{11} is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl or di-[(1-6C)alkyl]amino-(1-6C)alkyl;

$\mathbf{Z^2}$ is a C≡C or $C(R^{13})=C(R^{13})$ group, wherein each R^{13} group, which may be the same or different, is hydrogen or (1-6C)alkyl; and

$\mathbf{R^{14}}$ is selected from halogeno, cyano, isocyano, formyl, carboxy, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl, (1-6C)alkoxycarbonylamino-(1-6C)alkyl or from a group of the formula :

$$-X^7-Q^5$$

wherein X^7 is a direct bond or is selected from CO, $CH(OR^{15})$, $CON(R^{15})$ or $SO_2N(R^{15})$, wherein R^{15} is hydrogen or (1-6C)alkyl, and Q^5 is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any CH, CH_2 or CH_3 group within a R^{14} substituent optionally bears on each said CH, CH_2 or CH_3 group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, cyano, amino, carboxy, carbamoyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino, N-(1-6C)alkyl-(1-6C)alkanesulphonylamino or from a group of the formula :

$$-X^8-Q^6$$

wherein X^8 is a direct bond or is selected from O, S, SO, SO_2, $N(R^{16})$, CO, $CH(OR^{16})$, $CON(R^{16})$, $N(R^{16})CO$, $SO_2N(R^{16})$, $N(R^{16})SO_2$, $C(R^{16})_2O$, $C(R^{16})_2S$ and $N(R^{16})C(R^{16})_2$, wherein R^{16} is hydrogen or (1-6C)alkyl, and Q^6 is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any aryl, heteroaryl or heterocyclyl group within a substituent on R^{14} optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino, N-(1-6C)alkyl-(1-6C)alkanesulphonylamino or from a group of the formula :

$$-X^9-R^{17}$$

wherein X^9 is a direct bond or is selected from O and $N(R^{18})$, wherein R^{18} is hydrogen or (1-6C)alkyl, and R^{17} is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl, (1-6C)alkoxycarbonylamino-(1-6C)alkyl, or from a group of the formula :

$$-X^{10}-Q^7$$

wherein X^{10} is a direct bond or is selected from O, $N(R^{19})$ and CO, wherein R^{19} is hydrogen or (1-6C)alkyl, and Q^7 is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl and (1-6C)alkoxy,

and wherein any heterocyclyl group within a substituent on R^{14} optionally bears 1 or 2 oxo or thioxo substituents;

or a pharmaceutically-acceptable salt thereof.

In this specification the generic term "alkyl" includes both straight-chain and branched-chain alkyl groups such as propyl, isopropyl and tert-butyl, and also (3-7C)cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and

cycloheptyl. However references to individual alkyl groups such as "propyl" are specific for the straight-chain version only, references to individual branched-chain alkyl groups such as "isopropyl" are specific for the branched-chain version only and references to individual cycloalkyl groups such as "cyclopentyl" are specific for that 5-membered ring only. An analogous convention applies to other generic terms, for example (1-6C)alkoxy includes methoxy, ethoxy, cyclopropyloxy and cyclopentyloxy, (1-6C)alkylamino includes methylamino, ethylamino, cyclobutylamino and cyclohexylamino, and di-[(1-6Calkyl]amino includes dimethylamino, diethylamino, N-cyclobutyl-N-methylamino and N-cyclohexyl-N-ethylamino.

It is to be understood that, insofar as certain of the compounds of Formula I defined above may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention includes in its definition any such optically active or racemic form which possesses the above-mentioned activity. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Similarly, the above-mentioned activity may be evaluated using the standard laboratory techniques referred to hereinafter.

Suitable values for the generic radicals referred to above include those set out below.

A suitable value for any one of the 'Q' groups (Q^1 to Q^7) when it is aryl or for the aryl group within a 'Q' group is, for example, phenyl or naphthyl, preferably phenyl.

A suitable value for any one of the 'Q' groups (Q^1, Q^3, Q^5 or Q^6) when it is (3-7C)cycloalkyl or for the (3-7C)cycloalkyl group within a 'Q' group is, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or bicyclo[2.2.1]heptyl and a suitable value for any one of the 'Q' groups (Q^1, Q^3 or Q^6) when it is (3-7C)cycloalkenyl or for the (3-7C)cycloalkenyl group within a 'Q' group is, for example, cyclobutenyl, cyclopentenyl, cyclohexenyl or cycloheptenyl.

A suitable value for any one of the 'Q' groups (Q^1 to Q^7) when it is heteroaryl or for the heteroaryl group within a 'Q' group is, for example, an aromatic 5- or 6-membered monocyclic ring or a 9- or 10-membered bicyclic ring with up to five ring heteroatoms selected from oxygen, nitrogen and sulphur, for example furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazenyl, benzofuranyl, indolyl,

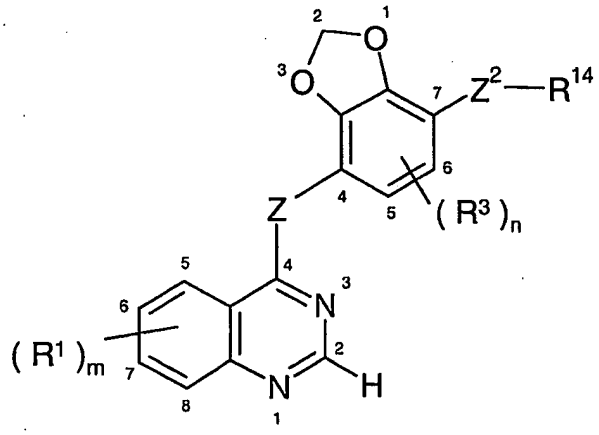
benzothienyl, benzoxazolyl, benzimidazolyl, benzothiazolyl, indazolyl, benzofurazanyl, quinolyl, isoquinolyl, quinazolinyl, quinoxalinyl, cinnolinyl or naphthyridinyl.

A suitable value for any one of the 'Q' groups (Q^1 to Q^7) when it is heterocyclyl or for the heterocyclyl group within a 'Q' group is, for example, a non-aromatic saturated or partially saturated 3 to 10 membered monocyclic or bicyclic ring with up to five heteroatoms selected from oxygen, nitrogen and sulphur, for example oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, oxepanyl, tetrahydrothienyl, 1,1-dioxotetrahydrothienyl, tetrahydrothiopyranyl, 1,1-dioxotetrahydrothiopyranyl, azetidinyl, pyrrolinyl, pyrrolidinyl, morpholinyl, tetrahydro-1,4-thiazinyl, 1,1-dioxotetrahydro-1,4-thiazinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl, dihydropyridinyl, tetrahydropyridinyl, dihydropyrimidinyl or tetrahydropyrimidinyl, preferably tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl, morpholinyl, 1,1-dioxotetrahydro-4H-1,4-thiazinyl, piperidinyl or piperazinyl. A suitable value for such a group which bears 1 or 2 oxo or thioxo substituents is, for example, 2-oxopyrrolidinyl, 2-thioxopyrrolidinyl, 2-oxoimidazolidinyl, 2-thioxoimidazolidinyl, 2-oxopiperidinyl, 2,5-dioxopyrrolidinyl, 2,5-dioxoimidazolidinyl or 2,6-dioxopiperidinyl.

A suitable value for a 'Q' group when it is heteroaryl-(1-6C)alkyl is, for example, heteroarylmethyl, 2-heteroarylethyl and 3-heteroarylpropyl. The invention comprises corresponding suitable values for 'Q' groups when, for example, rather than a heteroaryl-(1-6C)alkyl group, an aryl-(1-6C)alkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl-(1-6C)alkyl or heterocyclyl-(1-6C)alkyl group is present.

In structural Formula I there is a hydrogen atom at the 2-position on the quinazoline ring. It is to be understood thereby that the R^1 substituents may only be located at the 5-, 6-, 7- or 8-positions on the quinazoline ring *i.e.* that the 2-position remains unsubstituted. It is further to be understood that the R^3 group that may be present on the 1,3-benzodioxol-4-yl group within structural Formula I may be located on the phenyl ring or on the methylene group within the dioxol group. Preferably, any R^3 group that is present on the 1,3-benzodixol-4-yl group within structural Formula I is located on the phenyl ring thereof.

For the avoidance of doubt, the positions on structural Formula I are numbered as follows:



Suitable values for any of the 'R' groups (R^1 to R^{19}) or for various groups within an R^1, R^3 or R^{14} group include :-

for halogeno	fluoro, chloro, bromo and iodo;
for (1-6C)alkyl:	methyl, ethyl, propyl, isopropyl and tert-butyl;
for (2-8C)alkenyl:	vinyl, isopropenyl, allyl and but-2-enyl;
for (2-8C)alkynyl:	ethynyl, 2-propynyl and but-2-ynyl;
for (1-6C)alkoxy:	methoxy, ethoxy, propoxy, isopropoxy and butoxy;
for (2-6C)alkenyloxy:	vinyloxy and allyloxy;
for (2-6C)alkynyloxy:	ethynyloxy and 2-propynyloxy;
for (1-6C)alkylthio:	methylthio, ethylthio and propylthio;
for (1-6C)alkylsulphinyl:	methylsulphinyl and ethylsulphinyl;
for (1-6C)alkylsulphonyl:	methylsulphonyl and ethylsulphonyl;
for (1-6C)alkylamino:	methylamino, ethylamino, propylamino, isopropylamino and butylamino;
for di-[(1-6C)alkyl]amino:	dimethylamino, diethylamino, N-ethyl-N-methylamino and diisopropylamino;
for (1-6C)alkoxycarbonyl:	methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and tert-butoxycarbonyl;
for N-(1-6C)alkylcarbamoyl:	N-methylcarbamoyl, N-ethylcarbamoyl and N-propylcarbamoyl;
for N,N-di-[(1-6C)alkyl]carbamoyl:	N,N-dimethylcarbamoyl, N-ethyl-N-methylcarbamoyl and N,N-diethylcarbamoyl;
for (2-6C)alkanoyl:	acetyl and propionyl;
for (2-6C)alkanoyloxy:	acetoxy and propionyloxy;

for (2-6C)alkanoylamino: acetamido and propionamido;

for N-(1-6C)alkyl-(2-6C)alkanoylamino: N-methylacetamido and N-methylpropionamido;

for N-(1-6C)alkylsulphamoyl: N-methylsulphamoyl and N-ethylsulphamoyl;

for N,N-di-[(1-6C)alkyl]sulphamoyl: N,N-dimethylsulphamoyl;

for (1-6C)alkanesulphonylamino: methanesulphonylamino and ethanesulphonylamino;

for N-(1-6C)alkyl-(1-6C)alkanesulphonylamino: N-methylmethanesulphonylamino and N-methylethanesulphonylamino;

for (3-6C)alkenoylamino: acrylamido, methacrylamido and crotonamido;

for N-(1-6C)alkyl-(3-6C)alkenoylamino: N-methylacrylamido and N-methylcrotonamido;

for (3-6C)alkynoylamino: propiolamido;

for N-(1-6C)alkyl-(3-6C)alkynoylamino: N-methylpropiolamido;

for amino-(1-6C)alkyl: aminomethyl, 2-aminoethyl, 1-aminoethyl and 3-aminopropyl;

for (1-6C)alkylamino-(1-6C)alkyl: methylaminomethyl, ethylaminomethyl, 1-methylaminoethyl, 2-methylaminoethyl, 2-ethylaminoethyl and 3-methylaminopropyl;

for di-[(1-6C)alkyl]amino-(1-6C)alkyl: dimethylaminomethyl, diethylaminomethyl, 1-dimethylaminoethyl, 2-dimethylaminoethyl and 3-dimethylaminopropyl;

for halogeno-(1-6C)alkyl: chloromethyl, 2-chloroethyl, 1-chloroethyl and 3-chloropropyl;

for hydroxy-(1-6C)alkyl: hydroxymethyl, 2-hydroxyethyl, 1-hydroxyethyl and 3-hydroxypropyl;

for (1-6C)alkoxy-(1-6C)alkyl: methoxymethyl, ethoxymethyl, 1-methoxyethyl, 2-methoxyethyl, 2-ethoxyethyl and 3-methoxypropyl;

for cyano-(1-6C)alkyl: cyanomethyl, 2-cyanoethyl, 1-cyanoethyl and 3-cyanopropyl;

for (2-6C)alkanoylamino-(1-6C)alkyl: acetamidomethyl, propionamidomethyl and 2-acetamidoethyl; and

for (1-6C)alkoxycarbonylamino-(1-6C)alkyl: methoxycarbonylaminomethyl, ethoxycarbonylaminomethyl,

tert-butoxycarbonylaminomethyl and
2-methoxycarbonylaminoethyl.

A suitable value for $(R^1)_m$ when it is a (1-3C)alkylenedioxy group is, for example, methylenedioxy or ethylenedioxy and the oxygen atoms thereof occupy adjacent ring positions.

When, as defined hereinbefore, an R^1 group forms a group of the formula Q^1-X^1- and, for example, X^1 is a $OC(R^4)_2$ linking group, it is the carbon atom, not the oxygen atom, of the $OC(R^4)_2$ linking group which is attached to the quinazoline ring and the oxygen atom is attached to the Q^1 group. Similarly, when, for example a CH_3 group within a R^1 substituent bears a group of the formula -X^3-Q^3 and, for example, X^3 is a $C(R^7)_2O$ linking group, it is the carbon atom, not the oxygen atom, of the $C(R^7)_2O$ linking group which is attached to the CH_3 group and the oxygen atom is linked to the Q^3 group. A similar convention applies to the attachment of the groups of the formulae Q^3-X^3- and -X^8-Q^6.

As defined hereinbefore, adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent may be optionally separated by the insertion into the chain of a group such as O, $CON(R^5)$ or C≡C. For example, insertion of a C≡C group into the ethylene chain within a 2-morpholinoethoxy group gives rise to a 4-morpholinobut-2-ynyloxy group and, for example, insertion of a CONH group into the ethylene chain within a 3-methoxypropoxy group gives rise to, for example, a 2-(2-methoxyacetamido)ethoxy group.

When, as defined hereinbefore, any CH, CH_2 or CH_3 group within a R^1 or R^{14} substituent optionally bears on each said CH, CH_2 or CH_3 group one or more halogeno or (1-6C)alkyl substituents, there is suitably 1 halogeno or (1-6C)alkyl substituent present on each said CH group, there are suitably 1 or 2 such substituents present on each said CH_2 group and there are suitably 1, 2 or 3 such substituents present on each said CH_3 group.

When, as defined hereinbefore, any CH, CH_2 or CH_3 group within a R^1 or R^{14} substituent optionally bears on each said CH, CH_2 or CH_3 group a substituent as defined hereinbefore, suitable R^1 or R^{14} substituents so formed include, for example, hydroxy-substituted heterocyclyl-(1-6C)alkoxy groups such as 2-hydroxy-3-piperidinopropoxy and 2-hydroxy-3-morpholinopropoxy.

A suitable pharmaceutically-acceptable salt of a compound of the Formula I is, for example, an acid-addition salt of a compound of the Formula I, for example an acid-addition salt with an inorganic or organic acid such as hydrochloric, hydrobromic, sulphuric, trifluoroacetic, citric or maleic acid; or, for example, a salt of a compound of the Formula I

which is sufficiently acidic, for example an alkali or alkaline earth metal salt such as a calcium or magnesium salt, or an ammonium salt, or a salt with an organic base such as methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

Particular novel compounds of the invention include, for example, quinazoline derivatives of the Formula I, or pharmaceutically-acceptable salts thereof, wherein, unless otherwise stated, each of Z, m, R^1, n, R^3, Z^2 and R^{14} has any of the meanings defined hereinbefore or in paragraphs (a) to (q) hereinafter :-

(a) Z is O, S, SO, SO_2, CH_2 or NH;

(b) Z is O;

(c) Z is NH;

(d) R^1 substituents may only be located at the 5-, 6- and/or 7-positions on the quinazoline ring *i.e.* the 2- and 8-positions remain unsubstituted;

(e) R^1 substituents may only be located at the 6- and/or 7-positions on the quinazoline ring *i.e.* the 2-, 5- and 8-positions remain unsubstituted;

(f) m is 1 or 2, and each R^1 group, which may be the same or different, is selected from halogeno, trifluoromethyl, hydroxy, amino, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, or from a group of the formula :

$$Q^1-X^1-$$

wherein X^1 is a direct bond or is O and Q^1 is heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of an O,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more halogeno groups,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, (1-6C)alkyl, and (2-6C)alkanoyl, hydroxy and hydroxy(1-6C)alkyl,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo substituents;

(g) m is 1 or 2, and each R^1 group, which may be the same or different, is selected from methoxy, ethoxy, propoxy, isopropoxy, or from a group of the formula :

$$Q^1-X^1-$$

wherein X^1 is O and Q^1 is piperidino, piperidin-3-yl, piperidin-4-yl, 1-, 3- or 4-homopiperidinyl, piperazin-1-yl, homopiperazin-1-yl, 1-, 2- or 3-pyrrolidinylmethyl, morpholinomethyl, piperidinomethyl, 3- or 4-piperidinylmethyl, 1-, 3- or 4-homopiperidinylmethyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-2-ylpropyl, pyrrolidin-2-ylmethyl, 2-pyrrolidin-2-ylethyl, 3-pyrrolidin-1-ylpropyl, 4-pyrrolidin-1-ylbutyl, 2-morpholinoethyl, 3-morpholinopropyl, 4-morpholinobutyl, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethyl, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propyl, 2-piperidinoethyl, 3-piperidinopropyl, 4-piperidinobutyl, piperidin-4-ylmethyl, 2-piperidin-3-ylethyl, 3-piperidin-1-ylpropyl, 3-piperidin-3-ylpropyl, 2-piperidin-4-ylethyl, 3-piperidin-4-ylpropyl, 2-homopiperidin-1-ylethyl, 3-homopiperidin-1-ylpropyl, 2-piperazin-1-ylethyl, 3-piperazin-1-ylpropyl, 4-piperazin-1-ylbutyl, 2-homopiperazin-1-ylethyl or 3-homopiperazin-1-ylpropyl,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of a O,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more fluoro or chloro groups,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from methyl, ethyl, acetyl, hydroxy and hydroxymethyl,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo substituents;

(h) m is 2 and each R^1 group, which may be the same or different, is selected from methoxy, ethoxy, propoxy, isopropoxy, or from a group of the formula :

$$Q^1\text{-}X^1\text{-}$$

wherein X^1 is O and Q^1 is piperidino, piperidin-3-yl, piperidin-4-yl, 1-, 3- or 4-homopiperidinyl, piperazin-1-yl, homopiperazin-1-yl, 1-, 2- or 3-pyrrolidinylmethyl, morpholinomethyl, piperidinomethyl, 3- or 4-piperidinylmethyl, 1-, 3- or 4-homopiperidinylmethyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-2-ylpropyl, pyrrolidin-2-ylmethyl, 2-pyrrolidin-2-ylethyl, 3-pyrrolidin-1-ylpropyl, 4-pyrrolidin-1-ylbutyl, 2-morpholinoethyl, 3-morpholinopropyl, 4-morpholinobutyl, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethyl, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propyl, 2-piperidinoethyl, 3-piperidinopropyl, 4-piperidinobutyl, 2-piperidin-3-ylethyl, 3-piperidin-3-ylpropyl, piperidin-4-ylmethyl,

3-piperidin-1-ylpropyl, 2-piperidin-4-ylethyl, 3-piperidin-4-ylpropyl, 2-homopiperidin-1-ylethyl, 3-homopiperidin-1-ylpropyl, 2-piperazin-1-ylethyl, 3-piperazin-1-ylpropyl, 4-piperazin-1-ylbutyl, 2-homopiperazin-1-ylethyl or 3-homopiperazin-1-ylpropyl,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of a O,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more fluoro or chloro groups,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from methyl, ethyl, acetyl, hydroxy and hydroxymethyl,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo substituents;

(i) m is 2 and each R^1 group, which may be the same or different, is located at the 6- and 7-positions and R^1 is selected from methoxy, ethoxy, propoxy, isopropoxy, or from a group of the formula :

$$Q^1-X^1-$$

wherein X^1 is O and Q^1 is 1-, 2-, or 3-pyrrolidinyl, piperidino, piperidin-3-yl, piperidin-4-yl, 1-, 3- or 4-homopiperidinyl, piperazin-1-yl, homopiperazin-1-yl, 1-, 2- or 3-pyrrolidinylmethyl, morpholinomethyl, piperidinomethyl, 3- or 4-piperidinylmethyl, 1-, 3- or 4-homopiperidinylmethyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-2-ylpropyl, pyrrolidin-2-ylmethyl, 2-pyrrolidin-2-ylethyl, 3-pyrrolidin-1-ylpropyl, 4-pyrrolidin-1-ylbutyl, 2-morpholinoethyl, 3-morpholinopropyl, 4-morpholinobutyl, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethyl, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propyl, 2-piperidinoethyl, 3-piperidinopropyl, 4-piperidinobutyl, 2-piperidin-3-ylethyl, piperidin-4-ylmethyl, 3-piperidin-1-ylpropyl, 3-piperidin-3-ylpropyl, 2-piperidin-4-ylethyl, 3-piperidin-4-ylpropyl, 2-homopiperidin-1-ylethyl, 3-homopiperidin-1-ylpropyl, 2-piperazin-1-ylethyl, 3-piperazin-1-ylpropyl, 4-piperazin-1-ylbutyl, 2-homopiperazin-1-ylethyl or 3-homopiperazin-1-ylpropyl,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of a O,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more fluoro or chloro groups,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from methyl, ethyl, acetyl, hydroxy and hydroxymethyl,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo substituents;

(j) m is 2 and each R^1 group, which may be the same or different, is located at the 6- and 7-positions and is selected from methoxy or from a group of the formula :

$$Q^1-X^1-$$

wherein X^1 is O and Q^1 is selected from 3-pyrrolidinyl, 3-pyrrolidin-1-ylpropyl, piperidin-4-yl, piperidin-4-ylmethyl, 3-piperidin-1-ylpropyl, 3-morpholin-4-ylpropyl, 2-morpholin-4-ylethyl, 4-morpholin-4-ylbutyl, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propyl or 3-piperazin-1-ylpropyl,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 substituent selected from methyl, acetyl, hydroxy, hydroxymethyl and 2-fluoroethyl,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo substituents;

(k) m is 2 and one R^1 group which is located at the 6-position is methoxy and the second R^1 group is selected from a group of the formula :

$$Q^1-X^1-$$

wherein X^1 is O and Q^1 is selected from 3-morpholin-4-ylpropyl, 2-morpholin-4-ylethyl, 4-morpholin-4-ylbutyl, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propyl, 3-piperazin-1-ylpropyl, piperidin-4-ylmethyl, 3-piperidin-1-ylpropyl or 3-pyrrolidin-1-ylpropyl,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 substituent selected from methyl, acetyl, hydroxy, hydroxymethyl and 2-fluoroethyl,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo substituents;

(l) n is 0;

(m) n is 1 and the R^3 group is located at the 5- or 6-position of the 1,3-benzodioxol-4-yl group, especially the 6-position, and is selected from chloro, bromo, trifluoromethyl, cyano, hydroxy, methyl, ethyl, methoxy and ethoxy;

(n) Z^2 is a C≡C group;

(o) Z^2 is a CH=CH group;

(p) R^{14} is selected from cyano, carboxy, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, halogeno-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl or from a group of the formula :

$$-X^7-Q^5$$

wherein X^7 is a direct bond or CO and Q^5 is heterocyclyl or heterocyclyl-(1-6C)alkyl, and wherein any CH_2 or CH_3 group within a R^{14} substituent optionally bears on each said CH_2 or CH_3 group a (1-6C)alkoxy group,

and wherein any heterocyclyl group within a substituent on R^{14} optionally bears 1 or 2 oxo substituents; and

(q) R^{14} is methoxymethyl.

A particular compound of the invention is a quinazoline derivative of the Formula I wherein **Z** is NH

m is 2,

and the first R^1 group is a 6-methoxy group and the second R^1 group is located at the 7-position and is selected from methoxy, ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 3-morpholinopropoxy, 2-morpholin-4-ylethoxy, 4-morpholin-4-ylbutoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-fluoroethoxy, 3-[4-(2-fluoroethyl)piperazin-1-yl]propoxy, 3-(4-acetylpiperazin-1-yl)propoxy, 3-piperazin-1-ylpropoxy, -(4-methylpiperazin-1-yl)propoxy, 3-(3-oxopiperazin-1-yl)propoxy, 3-[4-(2-fluoroethylpiperazin-1-yl)propoxy, 3-(3-oxopiperazin-1-yl)propoxy, 2-(2-pyrrolidin-1-ylethoxy)ethoxy, 3-[2-(hydroxymethyl)pyrrolidin-1-yl]propoxy, 2-(2-methoxyethoxy)ethoxy, 3-chloropropoxy, 2-(2-chloroethoxy)ethoxy, 1-methylpiperidin-4-ylmethoxy or 3-(4-hydroxypiperidin-1-yl)propoxy,

n is 0 or 1 and R^3 group, if present, is located at the 5 position of the 1,3-benzodioxol group and is selected from fluoro or chloro;

Z^2 is a C≡C or CH=CH group; and

R^{14} is selected from cyano, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, halogeno-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl or from a group of the formula :

$$-X^7-Q^5$$

wherein X^7 is a direct bond or CO and Q^5 is heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any CH_2 or CH_3 group within a R^{14} substituent optionally bears on each said CH_2 or CH_3 group a (1-6C)alkoxy group;

or a pharmaceutically acceptable acid addition salt thereof.

A further particular compound of the invention is a quinazoline derivative of formula I wherein **Z** is NH

m is 2;

and the first $\mathbf{R^1}$ group is a 6-methoxy group and the second $\mathbf{R^1}$ group is located at the 7-position and is selected from 3-morpholino-4-ylpropoxy, 2-morpholin-4-ylethoxy, 4-morpholin-4-ylbutoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 3-(4-acetylpiperazin-1-yl)propoxy, 3-(4-methylpiperazin-1-yl)propoxy, 3-piperazin-1-ylpropoxy, 3-[4-(2-fluoroethylpiperazin-1-yl)propoxy, 3-(3-oxopiperazin-1-yl)propoxy, 1-methylpiperidin-4-yl)methoxy, 3-(4-hydroxypiperidin-1-yl)propoxy or 3-[2-(hydroxymethyl)pyrrolidin-1-yl]propoxy;

n is 0 or 1 and $\mathbf{R^3}$ group, if present, is located at the 5 position of the 1,3-benzodioxol group and is selected from fluoro or chloro;

$\mathbf{Z^2}$ is a C≡C or CH=CH group; and

$\mathbf{R^{14}}$ is methoxymethyl;

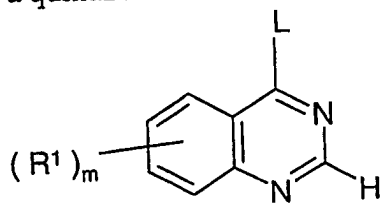
or a pharmaceutically acceptable acid addition salt thereof.

Particular compounds of the invention include, for example, the quinazoline derivatives of the Formula I described above hereinafter as examples 1, 2 and 3 and and also include 6-methoxy-*N*-[5-fluoro-7-(3-methoxyprop-1-ynyl)-1,3-benzodioxol-4-yl]-7-[3-morpholin-4-ylpropoxy]quinazolin-4-amine, 6-methoxy-*N*-[5-fluoro-7-(3-methoxyprop-1-ynyl)-1,3-benzodioxol-4-yl]-7-[3-(1,1-dioxothiomorpholin-4-yl)propoxy]quinazolin-4-amine, 6-methoxy-*N*-[5-fluoro-7-(3-methoxyprop-1-ynyl)-1,3-benzodioxol-4-yl]-7-[3-(4-acetylpiperazin-1-yl)propoxy]quinazolin-4-amine, 6-methoxy-*N*-[5-chloro-7-(3-methoxyprop-1-ynyl)-1,3-benzodioxol-4-yl]-7-[(1-methylpiperidin-4-yl)methoxy]quinazolin-4-amine,

A quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, may be prepared by any process known to be applicable to the preparation of chemically-related compounds. Such processes, when used to prepare a quinazoline derivative of the Formula I are provided as a further feature of the invention and are illustrated by the following representative process variants in which, unless otherwise stated, m, R^1, Z, n, R^3, Z^2 and R^{14} have any of the meanings defined hereinbefore. Necessary starting materials may be obtained by standard procedures of organic chemistry. The preparation of such starting materials is described in conjunction with the following representative process

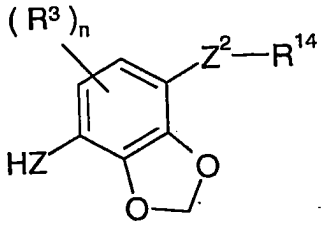
variants and within the accompanying Examples. Alternatively necessary starting materials are obtainable by analogous procedures to those illustrated which are within the ordinary skill of an organic chemist.

(a) For the production of those compounds of the Formula I wherein Z is an O, S or $N(R^2)$ group, the reaction of a quinazoline of the Formula II



II

wherein L is a displaceable group and m and R^1 have any of the meanings defined hereinbefore except that any functional group is protected if necessary, with a compound of the Formula III



III

wherein Z is O, S, or $N(R^2)$ and n, R^3, R^2, Z^2 and R^{14} have any of the meanings defined hereinbefore except that any functional group is protected if necessary, whereafter any protecting group that is present is removed by conventional means.

The reaction may conveniently be carried out in the presence of a suitable acid or in the presence of a suitable base. A suitable acid is, for example, an inorganic acid such as, for example, hydrogen chloride or hydrogen bromide. A suitable base is, for example, an organic amine base such as, for example, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, morpholine, N-methylmorpholine or diazabicyclo[5.4.0]undec-7-ene, or, for example, an alkali or alkaline earth metal carbonate or hydroxide, for example sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide, or, for example, an alkali metal amide, for example sodium hexamethyldisilazane or sodium bis(trimethylsilyl)amide or, for example, an alkali metal hydride, for example sodium hydride.

A suitable displaceable group L is, for example, a halogeno, alkoxy, aryloxy or sulphonyloxy group, for example a chloro, bromo, methoxy, phenoxy, pentafluorophenoxy,

methanesulphonyloxy or toluene-4-sulphonyloxy group. The reaction is conveniently carried out in the presence of a suitable inert solvent or diluent, for example an alcohol or ester such as methanol, ethanol, isopropanol or ethyl acetate, a halogenated solvent such as methylene chloride, chloroform or carbon tetrachloride, an ether such as tetrahydrofuran or 1,4-dioxan, an aromatic solvent such as toluene, or a dipolar aprotic solvent such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one or dimethylsulphoxide. The reaction is conveniently carried out at a temperature in the range, for example, 0 to 250°C, preferably in the range 0 to 120°C.

Typically, the quinazoline of the Formula II may be reacted with a compound of the Formula III in the presence of an aprotic solvent such as N,N-dimethylacetamide conveniently in the presence of a base, for example potassium carbonate, sodium hexamethyldisilazane, sodium bis(trimethylsilyl)amide and at a temperature in the range, for example, 0 to 150°C, preferably in the range, for example, 0 to 70°C.

The quinazoline derivative of the Formula I may be obtained from this process in the form of the free base or alternatively it may be obtained in the form of a salt with the acid of the formula H-L wherein L has the meaning defined hereinbefore. When it is desired to obtain the free base from the salt, the salt may be treated with a suitable base, for example, an organic amine base such as, for example, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, morpholine, N-methylmorpholine or diazabicyclo[5.4.0]undec-7-ene, or, for example, an alkali or alkaline earth metal carbonate or hydroxide, for example sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide.

Protecting groups may in general be chosen from any of the groups described in the literature or known to the skilled chemist as appropriate for the protection of the group in question and may be introduced by conventional methods. Protecting groups may be removed by any convenient method as described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

Specific examples of protecting groups are given below for the sake of convenience, in which "lower", as in, for example, lower alkyl, signifies that the group to which it is applied preferably has 1-4 carbon atoms. It will be understood that these examples are not exhaustive. Where specific examples of methods for the removal of protecting groups are given below

these are similarly not exhaustive. The use of protecting groups and methods of deprotection not specifically mentioned are, of course, within the scope of the invention.

A carboxy protecting group may be the residue of an ester-forming aliphatic or arylaliphatic alcohol or of an ester-forming silanol (the said alcohol or silanol preferably containing 1-20 carbon atoms). Examples of carboxy protecting groups include straight or branched chain (1-12C)alkyl groups (for example isopropyl, and tert-butyl); lower alkoxy- lower alkyl groups (for example methoxymethyl, ethoxymethyl and isobutoxymethyl); lower acyloxy-lower alkyl groups, (for example acetoxymethyl, propionyloxymethyl, butyryloxymethyl and pivaloyloxymethyl); lower alkoxycarbonyloxy-lower alkyl groups (for example 1-methoxycarbonyloxyethyl and 1-ethoxycarbonyloxyethyl); aryl-lower alkyl groups (for example benzyl, 4-methoxybenzyl, 2-nitrobenzyl, 4-nitrobenzyl, benzhydryl and phthalidyl); tri(lower alkyl)silyl groups (for example trimethylsilyl and tert-butyldimethylsilyl); tri(lower alkyl)silyl-lower alkyl groups (for example trimethylsilylethyl); and (2-6C)alkenyl groups (for example allyl). Methods particularly appropriate for the removal of carboxyl protecting groups include for example acid-, base-, metal- or enzymically-catalysed cleavage.

Examples of hydroxy protecting groups include lower alkyl groups (for example tert-butyl), lower alkenyl groups (for example allyl); lower alkanoyl groups (for example acetyl); lower alkoxycarbonyl groups (for example tert-butoxycarbonyl); lower alkenyloxycarbonyl groups (for example allyloxycarbonyl); aryl-lower alkoxycarbonyl groups (for example benzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl and 4-nitrobenzyloxycarbonyl); tri(lower alkyl)silyl (for example trimethylsilyl and tert-butyldimethylsilyl) and aryl-lower alkyl (for example benzyl) groups.

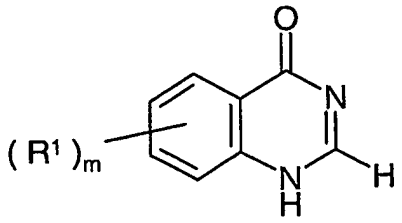
Examples of amino protecting groups include formyl, aryl-lower alkyl groups (for example benzyl and substituted benzyl, 4-methoxybenzyl, 2-nitrobenzyl and 2,4-dimethoxybenzyl, and triphenylmethyl); di-4-anisylmethyl and furylmethyl groups; lower alkoxycarbonyl (for example tert-butoxycarbonyl); lower alkenyloxycarbonyl (for example allyloxycarbonyl); aryl-lower alkoxycarbonyl groups (for example benzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl and 4-nitrobenzyloxycarbonyl); trialkylsilyl (for example trimethylsilyl and tert-butyldimethylsilyl); alkylidene (for example methylidene) and benzylidene and substituted benzylidene groups.

Methods appropriate for removal of hydroxy and amino protecting groups include, for example acid-, base-, metal- or enzymically-catalysed hydrolysis for groups such as

2-nitrobenzyloxycarbonyl, hydrogenation for groups such as benzyl and photolytically for groups such as 2-nitrobenzyloxycarbonyl.

The reader is referred to Advanced Organic Chemistry, 4th Edition, by J. March, published by John Wiley & Sons 1992, for general guidance on reaction conditions and reagents and to Protective Groups in Organic Synthesis, 2nd Edition, by T. Green *et al.*, also published by John Wiley & Son, for general guidance on protecting groups.

Quinazoline starting materials of the Formula II may be obtained by conventional procedures such as those disclosed in International Patent Applications WO 98/13354. For example, a 3,4-dihydroquinazolin-4-one of Formula IV,



IV

wherein m and R^1 have any of the meanings defined hereinbefore except that any functional group is protected if necessary, may be reacted with a halogenating agent such as thionyl chloride, phosphoryl chloride or a mixture of carbon tetrachloride and triphenylphosphine whereafter any protecting group that is present is removed by conventional means.

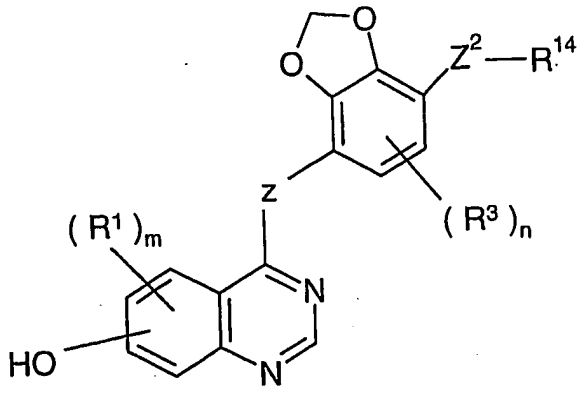
The 4-chloroquinazoline so obtained may be converted, if required, into a 4-(4-chloro-2-fluorophenoxy)quinazoline by reaction with 4-chloro-2-fluorophenol in the presence of a suitable base such as potassium carbonate and in the presence of a suitable solvent such as N,N-dimethylformamide.

1,3-Benzodioxol-4-amine starting materials (Formula III, for example when Z is NH) may be obtained by conventional procedures as illustrated in the Examples. Corresponding (Formula III, when Z is O or S) may be obtained by conventional procedures.

(b) For the production of those compounds of the Formula I wherein at least one R^1 group is a group of the formula

$$Q^1\text{-}X^1\text{-}$$

wherein Q^1 is an aryl-(1-6C)alkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl-(1-6C)alkyl or heterocyclyl-(1-6C)alkyl group or an optionally substituted alkyl group and X^1 is an oxygen atom, the coupling, conveniently in the presence of a suitable dehydrating agent, of a quinazoline of the Formula V



V

wherein m, R^1, Z, n, R^3, Z^2 and R^{14} have any of the meanings defined hereinbefore except that any functional group is protected if necessary, with an appropriate alcohol of the formula Q^1-OH wherein any functional group is protected if necessary, whereafter any protecting group that is present is removed by conventional means.

A suitable dehydrating agent is, for example, a carbodiimide reagent such as dicyclohexylcarbodiimide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide or a mixture of an azo compound such as diethyl or di-tert-butyl azodicarboxylate and a phosphine such as triphenylphosphine. The reaction is conveniently carried out in the presence of a suitable inert solvent or diluent, for example a halogenated solvent such as methylene chloride, chloroform or carbon tetrachloride and at a temperature in the range, for example, 10 to 150°C, preferably at or near ambient temperature.

The reaction is conveniently carried out in the presence of a suitable inert solvent or diluent, for example a halogenated solvent such as methylene chloride, chloroform or carbon tetrachloride and at a temperature in the range, for example, 10 to 150°C, preferably at or near ambient temperature.

(c) For the production of those compounds of the Formula I wherein R^1 is an amino-substituted (1-6C)alkoxy group (such as 2-homopiperidin-1-ylethoxy or 3-dimethylaminopropoxy), the reaction of a compound of the Formula I wherein R^1 is a halogeno-substituted (1-6C)alkoxy group with a heterocyclyl compound or an appropriate amine.

The reaction is conveniently carried out in the presence of a suitable inert diluent or carrier as defined hereinbefore and at a temperature in the range 10 to 150°C, preferably at or near ambient temperature.

(d) For the production of those compounds of the Formula I wherein an R^1 group contains a (1-6C)alkoxy or substituted (1-6C)alkoxy group or a (1-6C)alkylamino or substituted

(1-6C)alkylamino group, the alkylation, conveniently in the presence of a suitable base as defined hereinbefore, of a quinazoline derivative of the Formula I wherein the R^1 group contains a hydroxy group or a primary or secondary amino group as appropriate.

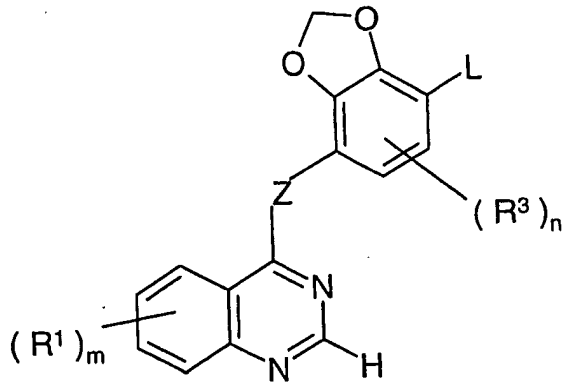
A suitable alkylating agent is, for example, any agent known in the art for the alkylation of hydroxy to alkoxy or substituted alkoxy, or for the alkylation of amino to alkylamino or substituted alkylamino, for example an alkyl or substituted alkyl halide, for example a (1-6C)alkyl chloride, bromide or iodide or a substituted (1-6C)alkyl chloride, bromide or iodide, conveniently in the presence of a suitable base as defined hereinbefore, in a suitable inert solvent or diluent as defined hereinbefore and at a temperature in the range, for example, 10 to 140°C, conveniently at or near ambient temperature.

Conveniently for the production of those compounds of the Formula I wherein R^1 contains a (1-6C)alkylamino or substituted (1-6C)alkylamino group, a reductive amination reaction may be employed. For example, for the production of those compounds of the Formula I wherein R^1 contains a N-methyl group, the corresponding compound containing a N-H group may be reacted with formaldehyde in the presence of a suitable reducing agent. A suitable reducing agent is, for example, a hydride reducing agent, for example an alkali metal aluminium hydride such as lithium aluminium hydride or, preferably, an alkali metal borohydride such as sodium borohydride, sodium cyanoborohydride, sodium triethylborohydride, sodium trimethoxyborohydride and sodium triacetoxyborohydride. The reaction is conveniently performed in a suitable inert solvent or diluent, for example tetrahydrofuran and diethyl ether for the more powerful reducing agents such as lithium aluminium hydride, and, for example, methylene chloride or a protic solvent such as methanol and ethanol for the less powerful reducing agents such as sodium triacetoxyborohydride and sodium cyanoborohydride. The reaction is performed at a temperature in the range, for example, 10 to 80°C, conveniently at or near ambient temperature.

(e) For the production of those compounds of the Formula I wherein Z is a SO or SO_2 group, wherein an R^1 or R^3 substituent is a (1-6C)alkylsulphinyl or (1-6C)alkylsulphonyl group or wherein an R^1, R^3 or R^{14} substituent contains a SO or SO_2 group, the oxidation of a compound of Formula I wherein Z is a S group or wherein an R^1 or R^3 substituent is a (1-6C)alkylthio group or wherein an R^1 R^3 or R^{14} substituent contains a S group as appropriate.

Conventional oxidation reagents and reaction conditions for such partial or complete oxidation of a sulphur atom are well known to the organic chemist.

(f) The reaction, conveniently in the presence of a suitable base as defined hereinbefore and in the presence of a suitable catalyst, of a compound of the Formula VI



VI

wherein L is a displaceable group as defined hereinbefore and m, R^1, Z, n and R^3 have any of the meanings defined hereinbefore except that any functional group is protected if necessary, with a compound of the Formula VII

$$HZ^2— R^{14} \qquad \text{VII}$$

wherein Z^2 is a C≡C or $C(R^{13})=C(R^{13})$ group and R^{13} and R^{14} have any of the meanings defined hereinbefore except that any functional group is protected if necessary, whereafter any protecting group that is present is removed by conventional means.

Conveniently the displaceable group is a halogeno group such as iodo, bromo or chloro. A suitable catalyst is, for example, an organometallic reagent, for example an organopalladium compound such as tetrakis(triphenylphosphine)palladium(0) or bis(triphenylphosphine)palladium(II) dichloride. The conversion reaction is conveniently carried out in the presence of a suitable inert diluent or carrier as defined hereinbefore and at a temperature in the range -30 to +120°C, depending on the substrate.

(g) For the production of a compound of the Formula I wherein R^{14} is a carboxy group, the cleavage of a compound of the Formula I wherein R^{14} is a (1-6C)alkoxycarbonyl group.

The cleavage reaction is conveniently carried out by the hydrolysis of the (1-6C)alkoxycarbonyl group in the presence of a suitable base, for example an alkali or alkaline earth metal carbonate or hydroxide such as sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide and in the presence of a suitable inert diluent or carrier as defined hereinbefore such as methanol and at a temperature in the range 10 to 150°C, conveniently at or near 40°C

(h) The reaction, conveniently in the presence of a suitable dehydrating agent as defined hereinbefore, of a compound of the Formula I wherein R^{14} is a carboxy group with an appropriate amine to form a further compound of the Formula I wherein R^{14} is a carbamoyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl or heterocyclylcarbonylamino group.

The reaction is conveniently carried out in the presence of a suitable inert diluent or carrier as defined hereinbefore and at a temperature in the range, for example, 10 to 150°C, preferably at or near ambient temperature.

When a pharmaceutically-acceptable salt of a quinazoline derivative of the Formula I is required, for example an acid-addition salt, it may be obtained by, for example, reaction of said quinazoline derivative with a suitable acid using a conventional procedure.

Biological Assays

The following assays can be used to measure the effects of the compounds as inhibitors of the MAPK pathway.

(a) Assay to detect MEK inhibition

To evaluate inhibitors of the MAPK pathway, a coupled assay was carried out which measures phosphorylation of serine/threonine residues present in the substrate in the presence or absence of inhibitor. Recombinant glutathione S-transferase fusion protein containing human p45MEK1 (GST-MEK) was activated by c-raf (Sf9 insect cell lysate from triple baculoviral infection with c-raf/ras/lck) and used for the assay. Active GST-MEK was first used to activate a recombinant glutathione S-transferase fusion protein containing p44MAP kinase (GST-MAPK) in the presence of ATP and Mg^{2+} for 60minutes at room temperature in the presence or absence of potential inhibitors. The activated GST-MAPK was then incubated with myelin basic protein (MBP) as substrate for 10 minutes at room temperature in the presence of ATP, Mg^{2+} and ^{33}P-ATP. The reaction was stopped by addition of 20% v/v phosphoric acid. Incorporation of ^{33}P into the myelin basic protein was determined by capture of the substrate on a filter mat, washing and counting using scintillation methods. The extent of inhibition was determined by comparison with untreated controls.

The final assay solution contained 10mM Tris, pH 7.5, 0.05mM EGTA, 8.33μM [$\gamma^{33}P$]ATP, 8.33mM $Mg(OAc)_2$, 0.5mM sodium orthovanadate, 0.05%w/v BSA, 6.5ng GST-MEK, 1μg GST-MAPK and 16.5μg MBP in a reaction volume of 60μl.

(b) In vitro MAP kinase assay

To determine whether compounds were inhibiting GST-MEK or GST-MAPK, a direct assay of MAPK activity was employed. GST-MAPK was activated by a constitutively active GST-MEK fusion protein containing two point mutations (S217E, S221E) and used for the assay in the presence and absence of potential inhibitors. The activated GST-MAPK was incubated with substrate (MBP) for 60min at room temperature in the presence of ATP, Mg^{2+} and ^{33}P-ATP. The reaction was stopped by addition of 20% v/v phosphoric acid. Incorporation of ^{33}P into the myelin basic protein was determined by capture of the substrate on a filter mat, washing and counting using scintillation methods.

The final assay solution contained 12mM Tris, pH 7.5, 0.06mM EGTA, 30μM [$\gamma^{33}P$]ATP, 10mM $Mg(OAc)_2$, 0.6mM sodium orthovanadate, 0.06%w/v BSA, 28ng GST-MAPK and 16.5μg MBP in a reaction volume of 60μl.

(c) Cell proliferation assays

Cells were seeded into multi-well plates at 20,000 - 40,000 cells/ml in growth medium containing 5% FCS and incubated overnight at 37°C. The compounds were prepared in fresh medium at an appropriate concentration and added to the wells containing the cells. These were then incubated for a further 72 hours. Cells were then either removed from the wells by incubating with trypsin/EDTA and counted using a Coulter counter, or treated with XTT/PMS in PBSA and optical densities read at 450nm.

The following assays can be used to measure the effects of the compounds of the present invention as c-Src tyrosine kinase inhibitors, as inhibitors in vitro of the proliferation of c-Src transfected fibroblast cells, as inhibitors in vitro of the migration of A549 human lung tumour cells and as inhibitors in vivo of the growth in nude mice of xenografts of A549 tissue.

(d) In Vitro Src Enzyme Assay

The ability of test compounds to inhibit the phosphorylation of a tyrosine containing polypeptide substrate by the enzyme c-Src kinase was assessed using a conventional Elisa assay.

A substrate solution [100μl of a 20μg/ml solution of the polyamino acid Poly(Glu, Tyr) 4:1 (Sigma Catalogue No. P0275) in phosphate buffered saline (PBS) containing 0.2mg/ml of sodium azide] was added to each well of a number of Nunc 96-well immunoplates (Catalogue No. 439454) and the plates were sealed and stored at 4°C for 16 hours. The excess of substrate solution was discarded, and aliquots of Bovine Serum Albumin (BSA; 150μl of a 5% solution in PBS) were transferred into each substrate-coated

assay well and incubated for 1 hour at ambient temperature to block non specific binding. The assay plate wells were washed in turn with PBS containing 0.05% v/v Tween 20 (PBST) and with Hepes pH7.4 buffer (50mM, 300µl/well) before being blotted dry.

Each test compound was dissolved in dimethyl sulphoxide and diluted with distilled water to give a series of dilutions (from 100µM to 0.001µM). Portions (25µl) of each dilution of test compound were transferred to wells in the washed assay plates. "Total" control wells contained diluted DMSO instead of compound. Aliquots (25µl) of an aqueous magnesium chloride solution (80mM) containing adenosine-5'-triphosphate (ATP; 40µM) was added to all test wells except the "blank" control wells which contained magnesium chloride without ATP.

Active human c-Src kinase (recombinant enzyme expressed in Sf9 insect cells; obtained from Upstate Biotechnology Inc. product 14-117) was diluted immediately prior to use by a factor of 1:10,000 with an enzyme diluent which comprised 100mM Hepes pH7.4 buffer, 0.2mM sodium orthovanadate, 2mM dithiothreitol and 0.02% BSA. To start the reactions, aliquots (50µl) of freshly diluted enzyme were added to each well and the plates were incubated at ambient temperature for 20 minutes. The supernatant liquid in each well was discarded and the wells were washed twice with PBST. Mouse IgG anti-phosphotyrosine antibody (Upstate Biotechnology Inc. product 05-321; 100µl) was diluted by a factor of 1:6000 with PBST containing 0.5% w/v BSA and added to each well. The plates were incubated for 1 hour at ambient temperature. The supernatant liquid was discarded and each well was washed with PBST (x4). Horse radish peroxidase (HRP)-linked sheep anti-mouse Ig antibody (Amersham Catalogue No. NXA 931; 100µl) was diluted by a factor of 1:500 with PBST containing 0.5% w/v BSA and added to each well. The plates were incubated for 1 hour at ambient temperature. The supernatant liquid was discarded and the wells were washed with PBST (x4).

A PCSB capsule (Sigma Catalogue No. P4922) was dissolved in distilled water (100ml) to provide phosphate-citrate pH5 buffer (50mM) containing 0.03% sodium perborate. An aliquot (50ml) of this buffer was mixed with a 50mg tablet of 2,2'-azinobis(3-ethylbenzothiazoline-6-sulphonic acid) (ABTS; Boehringer Catalogue No. 1204 521). Aliquots (100µl) of the resultant solution were added to each well. The plates were incubated for 20 to 60 minutes at ambient temperature until the optical density value of the "total" control wells, measured at 405nm using a plate reading spectrophotometer, was

approximately 1.0. "Blank" (no ATP) and "total" (no compound) control values were used to determine the dilution range of test compound which gave 50% inhibition of enzyme activity.

(e) In Vitro c-Src transfected NIH 3T3 (c-src 3T3) Fibroblast Proliferation Assay

This assay determined the ability of a test compound to inhibit the proliferation of National Institute of Health (NIH) mouse 3T3 fibroblast cells that had been stably-transfected with an activating mutant (Y530F) of human c-Src.

Using a similar procedure to that described by Shalloway *et al.*, Cell, 1987, 49, 65-73, NIH 3T3 cells were transfected with an activating mutant (Y530F) of human c-Src. The resultant c-Src 3T3 cells were typically seeded at 1.5×10^4 cells per well into 96-well tissue-culture-treated clear assay plates (Costar) each containing an assay medium comprising Dulbecco's modified Eagle's medium (DMEM; Sigma) plus 0.5% foetal calf serum (FCS), 2mM glutamine, 100 units/ml penicillin and 0.1mg/ml streptomycin in 0.9% aqueous sodium chloride solution. The plates were incubated overnight at 37°C in a humidified (7.5% CO_2 : 95% air) incubator.

Test compounds were solubilised in DMSO to form a 10mM stock solution. Aliquots of the stock solution were diluted with the DMEM medium described above and added to appropriate wells. Serial dilutions were made to give a range of test concentrations. Control wells to which test compound was not added were included on each plate. The plates were incubated overnight at 37°C in a humidified (7.5% CO_2 : 95% air) incubator.

BrdU labelling reagent (Boehringer Mannheim Catalogue No. 647 229) was diluted by a factor of 1:100 in DMEM medium containing 0.5% FCS and aliquots (20µl) were added to each well to give a final concentration of 10µM). The plates were incubated at 37°C for 2 hours. The medium was decanted. A denaturating solution (FixDenat solution, Boehringer Mannheim Catalogue No. 647 229; 50µl) was added to each well and the plates were placed on a plate shaker at ambient temperature for 45 minutes. The supernatant was decanted and the wells were washed with PBS (200µl per well). Anti-BrdU-Peroxidase solution (Boehringer Mannheim Catalogue No. 647 229) was diluted by a factor of 1:100 in PBS containing 1% BSA and 0.025% dried skimmed milk (Marvel (registered trade mark), Premier Beverages, Stafford, GB) and an aliquot (100µl) of the resultant solution was added to each well. The plates were placed on a plate shaker at ambient temperature for 90 minutes. The wells were washed with PBS (x5) to ensure removal of non-bound antibody conjugate. The plates were blotted dry and tetramethylbenzidine substrate solution (Boehringer Mannheim

Catalogue No. 647 229; 100µl) was added to each well. The plates were gently agitated on a plate shaker while the colour developed during a 10 to 20 minute period. The absorbance of the wells was measured at 690nm. The extent of inhibition of cellular proliferation at a range of concentrations of each test compound was determined and an anti-proliferative IC_{50} value was derived.

(f) In Vitro Microdroplet Migration Assay

This assay determines the ability of a test compound to inhibit the migration of adherent mammalian cell lines, for example the human tumour cell line A549.

RPMI medium(Sigma) containing 10% FCS, 1% L-glutamine and 0.3% agarose (Difco Catalogue No. 0142-01) was warmed to 37°C in a water bath. A stock 2% aqueous agar solution was autoclaved and stored at 42°C. An aliquot (1.5 ml) of the agar solution was added to RPMI medium (10 ml) immediately prior to its use. A549 cells (Accession No. ATCC CCL185) were suspended at a concentration of 2×10^7 cells/ml in the medium and maintained at a temperature of 37°C.

A droplet (2µl) of the cell/agarose mixture was transferred by pipette into the centre of each well of a number of 96-well, flat bottomed non-tissue-culture-treated microtitre plate (Bibby Sterilin Catalogue No. 642000). The plates were placed briefly on ice to speed the gelling of the agarose-containing droplets. Aliquots (90µl) of medium which had been cooled to 4°C were transferred into each well, taking care not to disturb the microdroplets. Test compounds were diluted from a 10mM stock solution in DMSO using RPMI medium as described above. Aliquots (10µl) of the diluted test compounds were transferred to the wells, again taking care not to disturb the microdroplets. The plates were incubated at 37°C in a humidified (7.5% CO_2 : 95% air) incubator for about 48 hours.

Migration was assessed visually and the distance of migration was measured back to the edge of the agar droplet. A migratory inhibitory IC_{50} was derived by plotting the mean migration measurement against test compound concentration.

(g) In Vivo A549 Xenograft Growth Assay

This test measures the ability of compounds to inhibit the growth of the A549 human carcinoma grown as a tumour in athymic nude mice (Alderley Park nu/nu strain). A total of about 5×10^6 A549 cells in matrigel (Beckton Dickinson Catalogue No. 40234) were injected subcutaneously into the left flank of each test mouse and the resultant tumours were allowed to grow for about 14 days. Tumour size was measured twice weekly using callipers and a

theoretical volume was calculated. Animals were selected to provide control and treatment groups of approximately equal average tumour volume. Test compounds were prepared as a ball-milled suspension in 1% polysorbate vehicle and dosed orally once daily for a period of about 28 days. The effect on tumour growth was assessed.

Although the pharmacological properties of the compounds of the Formula I vary with structural change as expected, in general activity possessed by compounds of the Formula I, may be demonstrated at the following concentrations or doses in one or more of the above tests (a) to (g) :-

Test (a):- IC_{50} in the range, for example, less than 4μM;

Test (b):- activity was observed in this screen;

Test (c):- IC_{50} in the range, for example, less than 30μM.

Test (d):- IC_{50} in the range, for example, 0.001 - 10 μM;

Test (d):- IC_{50} in the range, for example, 0.01 - 20 μM;

Test (f):- activity in the range, for example, 0.1-25 μM;

Test (g):- activity in the range, for example, 1-200 mg/kg/day;

No physiologically-unacceptable toxicity was observed in Test (g) at the effective dose for compounds tested of the present invention. Accordingly no untoward toxicological effects are expected when a compound of Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore is administered at the dosage ranges defined hereinafter.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier.

The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

The compositions of the invention may be obtained by conventional procedures using

conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 0.5 g of active agent (more suitably from 0.5 to 100 mg, for example from 1 to 30 mg) compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition.

The size of the dose for therapeutic or prophylactic purposes of a compound of the Formula I will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine.

In using a compound of the Formula I for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 0.1 mg/kg to 75 mg/kg body weight is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous administration, a dose in the range, for example, 0.1 mg/kg to 30 mg/kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, 0.05 mg/kg to 25 mg/kg body weight will be used. Oral administration is however preferred, particularly in tablet form. Typically, unit dosage forms will contain about 0.5 mg to 0.5 g of a compound of this invention.

According to a further aspect of the invention there is provided a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore for use in a method of treatment of the human or animal body by therapy.

As stated above we have found that the quinazoline derivatives of the present invention of Formula I possess potent anti-tumour activity which it is believed is obtained by way of inhibition of one or more of the MEK enzymes that are involved in the MAPK pathway.

Accordingly, the quinazoline derivatives of Formula I are of value as anti-proliferative agents in the containment and/or treatment of solid tumour disease. Particularly, the compounds of Formula I are expected to be useful in the prevention or treatment of those

tumours which are sensitive to inhibition of one or more of the MEK enzymes that are involved in the MAPK pathway. Further, the compounds of Formula I are expected to be useful in the prevention or treatment of those tumours which are mediated alone or in part by inhibition of the MEK enzymes *i.e.* the compounds may be used to produce a MEK enzyme inhibitory effect in a warm-blooded animal in need of such treatment. Specifically, the compounds of Formula I are expected to be useful in the prevention or treatment of solid tumour disease.

Thus, according to this aspect of the invention there is provided of a quinoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore for use as an anti-proliferative agent in the containment and/or treatment of solid tumour disease.

According to a further aspect of the invention there is provided the use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use as an anti-proliferative agent in the containment and/or treatment of solid tumour disease.

According to a further feature of the invention there is provided a method for producing an anti-proliferative effect by the containment and/or treatment of solid tumour disease in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

According to a further aspect of the invention there is provided the use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the prevention or treatment of solid tumour disease in a warm-blooded animals such as man.

According to a further feature of this aspect of the invention there is provided a method for the prevention or treatment of solid tumour disease in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a quinazoline derivative of the Formula 1, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

According to a further aspect of the invention there is provided the use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the prevention or treatment of those tumours which are sensitive to inhibition of MEK enzymes that are

involved in the MAPK pathway. Particular enzymes that the tumours may be sensitive to are MEK 1, MEK 2 and MEK 5.

According to a further feature of this aspect of the invention there is provided a method for the prevention or treatment of those tumours which are sensitive to inhibition of MEK enzymes that are involved in the MAPK pathway which comprises administering to said animal an effective amount of a quinazoline derivative of the Formula I, or a pharmaceutically- acceptable salt thereof, as defined hereinbefore.

According to a further aspect of the invention there is provided the use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in providing a MEK enzyme inhibitory effect.

According to a further feature of this aspect of the invention there is provided a method for providing a MEK enzyme inhibitory effect which comprises administering to said animal an effective amount of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

We have also found that the quinazoline derivatives of the present invention possess potent anti-tumour activity which it is believed is obtained by way of inhibition of one or more of the non-receptor tyrosine-specific protein kinases such as c-Src kinase that are involved in the signal transduction steps which lead to the invasiveness and migratory ability of metastasising tumour cells.

Particularly, the quinazoline derivatives of the present invention are of value as anti-invasive agents in the containment and/or treatment of solid tumour disease. Particularly, the compounds of the present invention are expected to be useful in the prevention or treatment of those tumours which are sensitive to inhibition of one or more of the multiple non-receptor tyrosine kinases such as c-Src kinase that are involved in the signal transduction steps which lead to the invasiveness and migratory ability of metastasising tumour cells. Further, the compounds of the present invention are expected to be useful in the prevention or treatment of those tumours which are mediated alone or in part by inhibition of the enzyme c-Src, *i.e.* the compounds may be used to produce a c-Src enzyme inhibitory effect in a warm-blooded animal in need of such treatment. Specifically, the compounds of the present invention are expected to be useful in the prevention or treatment of solid tumour disease.

According to this aspect of the invention there is provided a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore for use as an anti-invasive agent in the containment and/or treatment of solid tumour disease.

According to a further feature of this aspect of the invention there is provided the use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use as an anti-invasive agent in the containment and/or treatment of solid tumour disease.

According to a further feature of this aspect of the invention there is provided a method for producing an anti-invasive effect by the containment and/or treatment of solid tumour disease in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

According to a further aspect of the invention there is provided the use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the prevention or treatment of those tumours which are sensitive to inhibition of non-receptor tyrosine kinases such as c-Src kinase that are involved in the signal transduction steps which lead to the invasiveness and migratory ability of metastasising tumour cells.

According to a further feature of this aspect of the invention there is provided a method for the prevention or treatment of those tumours which are sensitive to inhibition of non-receptor tyrosine kinases such as c-Src kinase that are involved in the signal transduction steps which lead to the invasiveness and migratory ability of metastasising tumour cells which comprises administering to said animal an effective amount of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

According to a further aspect of the invention there is provided the use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in providing a c-Src kinase inhibitory effect.

According to a further feature of this aspect of the invention there is provided a method for providing a c-Src kinase inhibitory effect which comprises administering to said animal an effective amount of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

The anti-proliferative and anti-invasive treatment defined hereinbefore may be applied as a sole therapy or may involve, in addition to the quinazoline derivative of the invention, conventional surgery or radiotherapy or chemotherapy. Such chemotherapy may include one or more of the following categories of anti-tumour agents :-

(i) other anti-invasion agents (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function);

(ii) other anti-proliferative or antineoplastic drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan and nitrosoureas); antimetabolites (for example antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside and hydroxyurea, or, for example, one of the preferred antimetabolites disclosed in European Patent Application No. 562734 such as (2S)-2-{o-fluoro-p-[N-{2,7-dimethyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzamido}-4-(tetrazol-5-yl)butyric acid); antitumour antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol and taxotere); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecin);

(iii) cytostatic agents such as antioestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene and iodoxyfene), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrazole, vorazole and exemestane) and inhibitors of 5 α-reductase such as finasteride;

(iv) inhibitors of growth factor function, for example such inhibitors include growth factor antibodies, growth factor receptor antibodies, farnesyl transferase inhibitors, tyrosine kinase inhibitors and serine/threonine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example the EGFR tyrosine kinase inhibitors N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (ZD1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (CP 358774) and 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (CI 1033)), for

example inhibitors of the platelet-derived growth factor family and for example inhibitors of the hepatocyte growth factor family;

(v) antiangiogenic agents such as those which inhibit vascular endothelial growth factor such as the compounds disclosed in International Patent Applications WO 97/22596, WO 97/30035, WO 97/32856 and WO 98/13354 and those that work by other mechanisms (for example linomide, inhibitors of integrin $\alpha v\beta 3$ function and angiostatin);

(vi) antisense therapies, for example those which are directed to the targets listed above, such as ISIS 2503, an anti-ras antisense;

(vii) gene therapy approaches, including for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; and

(viii) immunotherapy approaches, including for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

According to this aspect of the invention there is provided a pharmaceutical product comprising a quinazoline derivative of the formula I as defined hereinbefore and an additional anti-tumour agent as defined hereinbefore for the conjoint treatment of cancer.

Although the compounds of the Formula I are primarily of value as therapeutic agents for use in warm-blooded animals (including man), they are also useful whenever it is required to inhibit the effects of the MEK enzymes that are involved in the MAPK kinase pathway or the effects of c Src. Thus, they are useful as pharmacological standards for use in the development of new biological tests and in the search for new pharmacological agents.

The invention will now be illustrated in the following Examples in which, generally :

(i) operations were carried out at ambient temperature, *i.e.* in the range 17 to 25°C and under an atmosphere of an inert gas such as argon unless otherwise stated;

(ii) evaporations were carried out by rotary evaporation *in vacuo* and work-up procedures were carried out after removal of residual solids by filtration;

(iii) column chromatography (by the flash procedure) and medium pressure liquid chromatography (MPLC) were performed on Merck Kieselgel silica (Art. 9385) or Merck Lichroprep RP-18 (Art. 9303) reversed-phase silica obtained from E. Merck, Darmstadt, Germany or high pressure liquid chromatography (HPLC) was performed on C18 reverse phase silica, for example on a Dynamax C-18 60Å preparative reversed-phase column;

(iv) yields, where present, are not necessarily the maximum attainable;

(v) in general, the end-products of the Formula I have satisfactory microanalyses and their structures were confirmed by nuclear magnetic resonance (NMR) and/or mass spectral techniques; fast-atom bombardment (FAB) mass spectral data were obtained using a Platform spectrometer and, where appropriate, either positive ion data or negative ion data were collected; NMR chemical shift values were measured on the delta scale [proton magnetic resonance spectra were determined using a Jeol JNM EX 400 spectrometer operating at a field strength of 400MHz, Varian Gemini 2000 spectrometer operating at a field strength of 300MHz or a Bruker AM300 spectrometer operating at a field strength of 300MHz]; the following abbreviations have been used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad;

(vi) intermediates were not generally fully characterised and purity was assessed by thin layer chromatographic, HPLC, infra-red (IR) and/or NMR analysis;

(vii) melting points are uncorrected and were determined using a Mettler SP62 automatic melting point apparatus or an oil-bath apparatus; melting points for the end-products of the Formula I were determined after crystallisation from a conventional organic solvent such as ethanol, methanol, acetone, ether or hexane, alone or in admixture;

(viii) the following abbreviations have been used:-

DMF	N,N-dimethylformamide
DMSO	dimethylsulphoxide
THF	tetrahydrofuran
DMA	N,N-dimethylacetamide

Example 1

6-methoxy-*N*-[7-(3-methoxyprop-1-ynyl)-1,3-benzodioxol-4-yl]-7-(3-morpholin-4-ylpropoxy)quinazolin-4-amine

Bis(Triphenyl-phosphine)palladium(II) chloride (94 mg), copper iodide (19 mg) and diisopropylamine (68 mg) were added to a stirred solution of *N*-(7-iodo-1,3-benzodioxol-4-yl)-6-methoxy-7-(3-morpholin-4-ylpropoxy)quinazolin-4-amine (200 mg) and methyl

propargyl ether (47 mg) in ethyl acetate (5mls) at –20°C. The reaction was allowed to warm to ambient temperature and stirred over 16 hours. The reaction mixture was partitioned between ethyl acetate and saturated $NaHCO_3$. The organic layer was washed with water and saturated brine and dried over magnesium sulfate. The product was purified by column chromatography on silica using a gradient of 0 – 10% methanol/methylene chloride as eluent. The resultant yellow gum was dissolved in minimal methylene chloride, diluted with diethyl ether and precipitated as an HCl salt by the addition of 1.0M ethereal hydrogen chloride. The resultant solid was centrifuged and washed with diethyl ether (3 times) and dried to give the title compound as a yellow solid (55 mg); NMR Spectrum: ($DMSOd_6$) 2.29 – 2.36 (m, 2H); 3.03 – 3.14 (m, 2H); 3.24 – 3.31 (m, 2H), 3.32 (s, 3H), 3.43 – 3.54 (m, 2H), 3.76 – 3.86 (m, 2H), 3.94 – 4.00 (m, 5H), 4.31 (t, 2H), 4.35 (s, 2H), 6.13 (s, 2H), 6.98 (d, 1H), 7.02 (d, 1H), 7.40 (s, 1H), 8.27 (s, 1H), 8.80 (s, 1H); Mass Spectrum: $M+H^+$ 507.11

The *N*-(7-iodo-1,3-benzodioxol-4-yl)-6-methoxy-7-(3-morpholin-4-ylpropoxy)quinazolin-4-amine used as a starting material was prepared as follows;

a) Preparation of 1,3-benzodioxol-4-amine

A mixture of 2,3-dihydroxybenzoic acid (5 g), methanol (50 ml) and concentrated sulphuric acid (10 drops) was stirred and heated to 60°C for 24 hours. The mixture was evaporated and the residue was taken up in ethyl acetate. The organic solution was washed with a saturated solution of sodium bicarbonate, dried over magnesium sulphate and evaporated to give methyl 2,3-dihydroxybenzoate (2.19 g); NMR Spectrum: ($CDCl_3$) 3.95 (s, 3H), 5.7 (s, 1H), 6.8 (t, 1H), 7.15 (d, H), 7.35 (d, H).

After repetition of the previous reaction, a mixture of methyl 2,3-dihydroxybenzoate (2.8 g), potassium fluoride (4.8 g) and DMF (45 ml) was stirred at ambient temperature for 30 minutes. Dibromomethane (1.28 ml) was added and the mixture was heated to 120°C for 3 hours. The mixture was cooled to ambient temperature, poured into water and extracted with diethyl ether. The organic phase was washed with water and with brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography using a 9:1 mixture of petroleum ether (b.p. 40-60°C) and ethyl acetate as eluent. There was thus obtained methyl 2,3-methylenedioxybenzoate (2.3 g) as a solid; NMR Spectrum: ($CDCl_3$) 3.95 (s, 3H), 6.1 (s, 2H), 6.85 (t, 1H), 7.0 (d, 1H), 7.45 (d, 1H).

A mixture of the material so obtained, a 2N aqueous potassium hydroxide solution (15.5 ml) and methanol (40 ml) was stirred at ambient temperature for 2 hours. The solution

was concentrated to about one quarter of the original volume and cooled in an ice bath. The mixture was acidified to pH 3.5 by the addition of a 2N aqueous hydrochloric acid solution. The resultant precipitate was collected by filtration and washed in turn with water and diethyl ether. There was thus obtained 2,3-methylenedioxybenzoic acid (1.87 g); NMR Spectrum: ($DMSOd_6$) 6.1 (s, 1H), 6.9 (t, 1H), 7.15 (d, 1H), 7.3 (d, 1H), 13.0 (br s, 1H).

The material so obtained was suspended in anhydrous dioxane (30 ml) and anhydrous diphenylphosphoryl azide (2.45 ml), triethylamine (1.6 ml) and tert-butanol (9 ml) were added. The mixture was heated to reflux for 5 hours. The mixture was cooled to ambient temperature, concentrated by evaporation and diluted with ethyl acetate. The organic phase was washed in turn with a 5% aqueous citric acid solution, water, an aqueous sodium bicarbonate solution and brine and dried over magnesium sulphate. The solvent was evaporated and the residue was purified by column chromatography on silica using a 19:1 mixture of petroleum ether (b.p. 40-60°C) and ethyl acetate as eluent. There was thus obtained tert-butyl 2,3-methylenedioxyphenylcarbamate (1.98 g) as a solid; NMR Spectrum: ($CDCl_3$) 1.55 (s, 9H), 5.95 (s, 2H), 6.4 (br s, 1H), 6.55 (d, 1H), 6.8 (t, 1H), 7.45 (d, 1H).

A 5N aqueous hydrochloric acid solution (30 ml) was added to a solution of tert-butyl 2,3-methylenedioxyphenylcarbamate (1.9 g) in ethanol (38 ml) and the reaction mixture was stirred at ambient temperature for 20 hours. The ethanol was evaporated and the residual aqueous phase was washed with diethyl ether and neutralised to pH7 by the addition of solid potassium hydroxide. The resultant mixture was filtered and the aqueous phase was extracted with diethyl ether. The organic phase was washed with brine, dried over magnesium sulphate and evaporated. There was thus obtained 1,3-benzodioxol-4-amine (1.0 g) as an oil; NMR Spectrum: ($CDCl_3$) 3.0 (br s, 2H), 5.9 (s, 2H), 6.3 (m, 2H), 7.25 (t, 1H).

b) Preparation of 7-iodo-1,3-benzodioxol-4-amine

Benzyltrimethylammonium dichloroiodate (2.8 g) was added portionwise over 10 minutes to a stirred mixture of 1,3-benzodioxol-4-amine (1 g), calcium carbonate (0.95 g) in methanol (5 ml) and dichloromethane (10 ml). The reaction mixture was stirred at ambient temperature for 1.5 hours. The reaction mixture was diluted with water and extracted with dichloromethane. The organics were washed with water saturated brine and dried over magnesium sulfate. The residue was purified by column chromatography on silica using a gradient of an 8 :1 mixture of dichloromethane/isohexane to Dichloromethane as eluent. There was thus obtained 7-iodo-1,3-benzodioxol-4-amine as a beige crystalline solid (1.1 g); NMR Spectrum: ($DMSOd_6$) 5.04 (bs, 2H); 5.94 (s, 2H); 6.13 (d, 1H), 6.80 (d, 1H).

c) Preparation of 4-chloro-6-methoxy-7-(3-morpholin-4-ylpropoxy)quinazoline

A mixture of 2-amino-4-benzyloxy-5-methoxybenzamide (J. Med. Chem., 1977, 20, 146-149; 10 g), (3-dimethylamino-2-azaprop-2-en-1-ylidene)dimethylammonium chloride (Gold's reagent, 7.4 g) and dioxane (100 ml) was stirred and heated to reflux for 24 hours. Sodium acetate (3.02 g) and acetic acid (1.65 ml) were added and the reaction mixture was heated for a further 3 hours. The mixture was evaporated and water was added to the residue. The resultant solid was collected by filtration, washed with water and dried. The material was recrystallised from acetic acid to give 7-benzyloxy-6-methoxy-3,4-dihydroquinazolin-4-one (8.7 g).

After repetition of the reaction so described, a mixture of 7-benzyloxy-6-methoxy-3,4-dihydroquinazolin-4-one (35 g), thionyl chloride (440 ml) and DMF (1.75 ml) was heated to reflux for 4 hours. The thionyl chloride was evaporated under vacuum and the residue was azeotroped with toluene three times. The residue was dissolved in N-methylpyrrolidin-2-one (250 ml) to give a solution of 7-benzyloxy-4-chloro-6-methoxyquinazoline.

Phenol (29.05 g) was dissolved in N-methylpyrrolidin-2-one (210 ml) and sodium hydride (60% dispersion in mineral oil; 11.025 g) was added in portions with cooling. The resultant mixture was stirred at ambient temperature for 3 hours. The resultant viscous suspension was diluted with N-methylpyrrolidin-2-one (180 ml) and stirred overnight. The above-mentioned solution of 7-benzyloxy-4-chloro-6-methoxyquinazoline was added and the resultant suspension was stirred and heated to 100°C for 2.5 hours. The mixture was allowed to cool to ambient temperature and poured into water (1.5 L) with vigorous stirring. The precipitate was collected by filtration, washed with water and dried under vacuum. The material so obtained was dissolved in methylene chloride and the solution was washed with brine and filtered through phase separating paper. The solution was evaporated under vacuum and the resultant residue was triturated under diethyl ether. There was thus obtained 7-benzyloxy-6-methoxy-4-phenoxyquinazoline (87.8 g); NMR Spectrum: ($CDCl_3$) 4.09 (s, 3H), 5.34 (s, 2H), 7.42 (m, 12H), 7.63 (s, 1H).

A mixture of a portion (36.95 g) of the material so obtained and trifluoroacetic acid (420 ml) was heated to reflux for 3 hours. The reaction mixture was allowed to cool and evaporated under vacuum. The residue was stirred mechanically under water, basified by the addition of a saturated aqueous sodium bicarbonate solution and stirred overnight. The water was decanted and the residual solid was suspended in acetone. After stirring, the white solid was collected by filtration, washed with acetone and dried to give 7-hydroxy-6-methoxy-

4-phenoxyquinazoline (26.61 g); NMR Spectrum: ($DMSOd_6$) 3.97 (s, 3H), 7.22 (s, 1H), 7.3 (m, 3H), 7.47 (t, 2H), 7.56 (s, 1H), 8.47 (s, 1H), 10.7 (s, 1H).

A mixture of 7-hydroxy-6-methoxy-4-phenoxyquinazoline (25.27 g), 3-morpholinopropyl chloride (18.48 g), potassium carbonate (39.1 g) and DMF (750 ml) was stirred and heated to 90°C for 3 hours. The mixture was allowed to cool to ambient temperature and filtered. The filtrate was evaporated and the residue was triturated under ethyl acetate. There was thus obtained 6-methoxy-7-(3-morpholin-4-ylpropoxy)-4-phenoxyquinazoline (31.4 g); NMR Spectrum: ($DMSOd_6$) 1.97 (m, 2H), 2.39 (t, 4H), 2.47 (t, 2H), 3.58 (t, 4H), 3.95 (s, 3H), 4.23 (t, 2H), 7.31 (m, 3H), 7.36 (s, 1H), 7.49 (t, 2H), 7.55 (s, 1H), 8.52 (s, 1H).

A mixture of the material so obtained and 6N aqueous hydrochloric acid solution (800 ml) was stirred and heated to reflux for 1.5 hours. The reaction mixture was decanted and concentrated to a volume of 250 ml. The mixture was basified to pH9 by the addition of a saturated aqueous sodium bicarbonate solution and extracted with methylene chloride (4x400 ml). The combined extracts were filtered through phase separating paper and the filtrate was evaporated. The resultant solid was triturated under ethyl acetate to give 6-methoxy-7-(3-morpholin-4-ylpropoxy)-3,4-dihydroquinazolin-4-one (23.9 g); NMR Spectrum: ($DMSOd_6$) 1.91 (m, 2H), 2.34 (t, 4H), 2.42 (t, 2H), 3.56 (t, 4H), 3.85 (s, 3H), 4.12 (t, 2H), 7.11 (s, 1H), 7.42 (s, 1H), 7.96 (s, 1H), 12.01 (s, 1H).

A mixture of the material so obtained, thionyl chloride (210 ml) and DMF (1.8 ml) was heated to reflux for 1.5 hours. The thionyl chloride was removed by evaporation under vacuum and the residue was azeotroped with toluene three times. The residue was taken up in water and basified to pH8 by the addition of a saturated aqueous sodium bicarbonate solution. The resultant aqueous layer was extracted with methylene chloride (4x400 ml). The combined extracts were washed with water and with brine and dried over magnesium sulphate. The solution was filtered and evaporated. The resultant solid was triturated under ethyl acetate to give 4-chloro-6-methoxy-7-(3-morpholin-4-ylpropoxy)quinazoline (17.39 g); NMR Spectrum: ($CDCl_3$) 2.1-2.16 (m, 2H), 2.48 (br s, 4H), 2.57 (t, 2H), 3.73 (t, 4H), 4.05 (s, 3H), 4.29 (t, 2H), 7.36 (s, 1H), 7.39 (s, 1H), 8.86 (s, 1H).

The 3-morpholinopropyl chloride used as a reagent was obtained as follows :-

A mixture of morpholine (52.2 ml), 1-bromo-3-chloropropane (30 ml) and toluene (180 ml) was heated to 70°C for 3 hours. The solid was removed by filtration and the filtrate was evaporated under vacuum. The resultant oil was decanted from the additional solid which

was deposited and the oil was purified by vacuum distillation to yield 3-morpholinopropyl chloride (37.91 g); NMR Spectrum: ($DMSOd_6$) 1.85 (m, 2H), 2.3 (t, 4H), 2.38 (t, 2H), 3.53 (t, 4H), 3.65 (t, 2H).

4.0M HCl in Dioxane (0.37 ml) was added to a stirred suspension of 4-chloro-6-methoxy-7-(3-morpholin-4-ylpropoxy)quinazoline (500 mg) and 7-iodo-1,3-benzodioxol-4-amine (0.39 g) in DMA (1 ml). The resultant mixture was stirred and heated to 80°C for 10mins. A grey precipitate was formed which was filtered and washed with further DMA followed by diethyl ether and dried to give *N*-(7-iodo-1,3-benzodioxol-4-yl)-6-methoxy-7-(3-morpholin-4-ylpropoxy)quinazolin-4-amine as a beige solid (0.59 g); NMR Spectrum: ($DMSOd_6$) 2.29 – 2.37 (m, 2H); 3.03 – 3.14 (m, 2H); 3.22 – 3.30 (m, 2H), 3.40 – 3.51 (m, 2H), 3.78 – 3.88 (m, 2H), 3.94 – 4.00 (m, 5H), 4.31 (t, 2H), 6.11 (s, 2H), 6.80 (d, 1H), 7.27 (d, 1H), 7.41 (s, 1H), 8.29 (s, 1H), 8.78 (s, 1H); Mass Spectrum: $M+H^+$ 562.9.

Example 2

***N*-[5-chloro-7-(3-methoxyprop-1-ynyl)-1,3-benzodioxol-4-yl]-6-methoxy-7-(3-morpholin-4-ylpropoxy)quinazolin-4-amine**

Sodium hexamethyldisilazane (1M solution in THF; 1.0 ml) was added to a mixture of 4-chloro-6-methoxy-7-(3-morpholin-4-ylpropoxy)quinazoline (0.16 g) and 5-chloro-7-(3-methoxyprop-1-ynyl)-1,3-benzodioxol-4-amine (0.12 g) in DMA (5 ml) that was cooled to 0°C. The resultant mixture was stirred and allowed to warm to ambient temperature for 2 hours. The reaction mixture was reduced in vacuo and partitioned between ethylacetate and water. The organic layers were washed with water and brine and the product was purified column chromatography on silica using a gradient of 0 – 10% methanol/methylene chloride as eluent. The resultant yellow gum was dissolved in minimal methylene chloride, diluted with diethyl ether and precipitated as an HCl salt by the addition of 1.0M ethereal HCl. The resultant solid was centrifuged and washed with diethyl ether (3 times) and dried to give the title compound as a yellow solid (185 mg); NMR Spectrum: ($DMSOd_6$ + CD_3CO_2D at 100°C) 2.33 – 2.40 (m, 2H), 3.30 – 3.40 (m, 9H), 3.93 – 3.98 (m, 4H), 4.03 (s, 3H), 4.38 – 4.41 (m, 4H), 6.19 (s, 2H), 7.15 (s, 1H), 7.41 (s, 1H), 8.16 (s, 1H), 8.66 (s, 1H); Mass Spectrum: $M+H^+$ 541.5.

The starting material were prepared as follows :-

a) 4-chloro-6-methoxy-7-(3-morpholin-4-ylpropoxy)quinazoline was prepared as described in example 1 above

b) Preparation of 5-chloro-7-(3-methoxyprop-1-ynyl)-1,3-benzodioxol-4-amine

Sulphuryl chloride (72.5 ml) was added dropwise during 1.7 hours to a stirred mixture of benzodioxole (100 g), aluminium trichloride (0.43 g) and diphenyl sulphide (0.55 ml). Once the reaction started with the evolution of sulphur dioxide, the reaction mixture was cooled in a water bath to a temperature of approximately 22°C. After completion of the addition, the reaction mixture was stirred at ambient temperature for 45 minutes. The reaction mixture was degassed under vacuum and filtered and the filtrate was distilled at atmospheric pressure using a Vigreux distillation column. There was thus obtained 5-chloro-1, 3-benzodioxole; b.p. 185-187°C; NMR Spectrum: ($CDCl_3$) 6.0 (s, 2H); 6.7 (d, 1H); 6.75-6.9 (m, 2H).

A mixture of diisopropylamine (4.92 ml) and THF (100 ml) was cooled to -78°C and n-butyllithium (2.5 M in hexane, 14 ml) was added dropwise. The mixture was stirred at -78°C for 15 minutes. 5-Chloro-1, 3-benzodioxole (3.73 ml) was added dropwise and the reaction mixture was stirred at -78°C for 30 minutes. Dry carbon dioxide gas was bubbled into the reaction mixture for 30 minutes. The resultant reaction mixture was allowed to warm to ambient temperature and was stirred for a further hour. Water was added and the organic solvent was evaporated. The residue was acidified to pH2 by the addition of 2N aqueous hydrochloric acid solution. The resultant solid was isolated and washed in turn with water and diethyl ether. There was thus obtained 5-chloro-1,3-benzodioxole-4-carboxylic acid (5.4 g); NMR Spectrum: ($DMSOd_6$) 6.15 (s, 2H), 7.0 (m, 2H), 13.7 (br s, 1H).

A portion (1g) of the material so obtained was dissolved in 1,4-dioxane (15 ml) and anhydrous tert-butanol (4 ml), diphenylphosphoryl azide (1.12 ml) and triethylamine (0.73 ml) were added in turn. The resultant mixture was stirred and heated to 100°C for 4 hours. The mixture was evaporated and the residue was partitioned between ethyl acetate and a 5% aqueous citric acid solution. The organic phase was washed in turn with water, a saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using a 9:1 mixture of petroleum ether (b.p. 40-60°C) and ethyl acetate as eluent. There was thus obtained tert-butyl 5-chloro-1,3-benzodioxol-4-ylcarbamate (1.1 g); NMR Spectrum: ($DMSOd_6$) 1.45 (s, 9H), 6.1 (s, 2H), 6.85 (d, 1H), 6.95 (d, 1H), 8.75 (s, 1H).

A mixture of the material so obtained (1.1 g), trifluoroacetic acid (6 ml) and methylene chloride (20 ml) was stirred at ambient temperature for 3 hours. The solvent was evaporated and the residue was partitioned between ethyl acetate and a saturated aqueous sodium

bicarbonate solution. The organic phase was washed with brine, dried over magnesium sulphate and evaporated. There was thus obtained 5-chloro-1,3-benzodioxol-4-amine (0.642 g); NMR Spectrum: ($DMSOd_6$) 5.15 (s, 2H), 6.0 (s, 2H), 6.25 (d, 1H), 6.75 (d, 1H).

Benzyltrimethylammonium dichloroiodate (6.7 g) was added portionwise over 10 minutes to a stirred mixture of 5-chloro-1,3-benzodioxol-4-amine (3 g), calcium carbonate (2.28 g) in methanol (15 ml) and dichloromethane (30 ml). The reaction mixture was stirred at ambient temperature for 1.5 hours. The reaction mixture was diluted with water and extracted with dichloromethane. The organics were washed with water, saturated brine and dried over magnesium sulfate. . The residue was purified by column chromatography on silica using a gradient of an 8 :1 mixture of dichloromethane/isohexane to dichloromethane as eluent. There was thus obtained 5-chloro-7-iodo-1,3-benzodioxol-4-amine as a black crystalline solid (4.82 g); NMR Spectrum: ($DMSOd_6$) 6.04 (s, 2H), 7.00 (s, 1H).

Bis(Triphenyl-phosphine)palladium(II) chloride (472 mg), copper iodide (192 mg) and diisopropylamine (680 mg) were added to a stirred solution of 5-chloro-7-iodo-1,3-benzodioxol-4-amine (1000 mg) and methyl propargyl ether (471 mg) in ethyl acetate (10mls) at –20°C. The reaction was allowed to warm to ambient temperature over 16 hours. The reaction mixture was partitioned between Ethyl acetate and saturated NaHCO3. The organics were washed with water and saturated brine and dried over magnesium sulfate. The product was purified by column chromatography on silica using a gradient of 80 – 100% Dichloromethane/isohexane as eluent. The 5-chloro-7-(3-methoxyprop-1-ynyl)-1,3-benzodioxol-4-amine product.was thus obtained as a tan crystalline solid (200 mg); NMR Spectrum: ($DMSOd_6$) 3.28 (s, 3H), 4.26 (s, 2H), 5.52 (s, 2H), 6.05 (s, 2H), 6.93 (s, 1H).

Example 3

6-methoxy-*N*-[5-chloro-7-(3-methoxyprop-1-ynyl)-1,3-benzodioxol-4-yl]-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazolin-4-amine

A solution of sodium bis(trimethylsilyl)amide (1.33ml) in tetrahydrofuran (1.0Mol/L, 1.33mmol) was added to a solution of 4-chloro-6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinazoline (0.212g) and 5-chloro-7-(3-methoxyprop-1-ynyl)-1,3-benzodioxol-4-amine (0.16g) in DMF (3 ml) cooled to 0°C under a nitrogen atmosphere. The reaction mixture was stirred for 1.5 hours. The reaction mixture was diluted with a saturated solution of ammonium chloride and extracted twice with ethyl acetate. The organic phases were combined and dried over magnesium sulfate and evaporated *in vacuo*. The residue was

purified by column chromatography on silica using increasingly polar mixtures of dichloromethane and methanol as the eluent to give the title compound as a light brown solid (0.22g). NMR Spectrum: 1.93 (m, 2H), 2.12 (s, 3H), 2.22-2.50 (m, 10H), 3.36 (s, 3H), 3.93 (s, 3H), 4.17 (t, 2H), 4.35 (s, 2H), 6.14 (s, 2H), 7.14 (s, 1H), 7.15 (s, 1H), 7.80 (s, 1H), 8.29 (s, 1H), 9.49 (s, 1H); Mass Spectrum: M+H+ 554, M+H- 552.

The starting materials were prepared as follows:-

a) 5-chloro-7-(3-methoxyprop-1-ynyl)-1,3-benzodioxol-4-amine was prepared as described in example 2

b) Preparation of 4-chloro-6-methoxy-7-(3-(4-methylpiperazin-1-yl)propoxy)quinazoline

3-(4-Methylpiperazin-1-yl)propyl 4-toluenesulphonate was prepared as follows :-

A mixture of 3-bromopropanol (20 ml), N-methylpiperazine (29 ml), potassium carbonate (83 g) and ethanol (200 ml)was stirred and heated to reflux for 20 hours. The mixture was cooled to ambient temperature and filtered. The filtrate was evaporated and the residue was triturated under diethyl ether. The resultant mixture was filtered and the filtrate was evaporated. The residue was purified by distillation at about 60-70°C under about 0.2 mm Hg to give 1-(3-hydroxypropyl)-4-methylpiperazine (17 g); NMR Spectrum: ($CDCl_3$) 1.72 (m, 2H), 2.3 (s, 3H), 2.2-2.8 (m, 8H), 2.6 (t, 2H), 3.8 (t, 2H), 5.3 (br s, 1H).

4-Toluenesulphonyl chloride (3.2 g) was added to a stirred mixture of 1-(3-hydroxypropyl)-4-methylpiperazine (2.4 g), triethylamine (4.6 ml) and methylene chloride (60 ml) and the resultant mixture was stirred at ambient temperature for 2 hours. The solution was washed in turn with a saturated aqueous sodium bicarbonate solution and with water and filtered through phase separating paper. The organic filtrate was evaporated to give 3-(4-methylpiperazin-1-yl)propyl 4-toluenesulphonate as an oil which crystallised on standing (3.7 g); Mass Spectrum: $M+H^+$ 313.

The trifluoroacetic acid salt of 4-(4-chloro-2-fluorophenoxy)-7-hydroxy-6-methoxyquinazoline was prepared as follows :-

A mixture of 2-amino-4-benzyloxy-5-methoxybenzamide (J. Med. Chem., 1977, 20, 146-149; 10 g), (3-dimethylamino-2-azaprop-2-en-1-ylidene)dimethylammonium chloride (Gold's reagent, 7.4 g) and dioxane (100 ml) was stirred and heated to reflux for 24 hours. Sodium acetate (3.02 g) and acetic acid (1.65 ml) were added and the reaction mixture was heated for a further 3 hours. The mixture was evaporated and water was added to the residue. The resultant solid was collected by filtration, washed with water and dried. The material was

recrystallised from acetic acid to give 7-benzyloxy-6-methoxy-3,4-dihydroquinazolin-4-one (8.7 g).

After repetition of the reaction so described, a mixture of 7-benzyloxy-6-methoxy-3,4-dihydroquinazolin-4-one (20.3 g), thionyl chloride (440 ml) and DMF (1.75 ml) was heated to reflux for 4 hours. The thionyl chloride was evaporated under vacuum and the residue was azeotroped with toluene three times to give 7-benzyloxy-4-chloro-6-methoxyquinazoline.

A mixture of the 7-benzyloxy-4-chloro-6-methoxyquinazoline so obtained, potassium carbonate (50 g) and 4-chloro-2-fluorophenol (8.8 ml) and DMF (500 ml) was stirred and heated to 100°C for 5 hours. The mixture was allowed to cool to ambient temperature, poured into water (2 L) and stirred at ambient temperature for a few minutes. The resultant solid was isolated and washed with water. The solid was dissolved in methylene chloride and the solution was filtered and treated with decolourising charcoal. The resultant solution was filtered and evaporated to give a solid which was triturated under diethyl ether. There was thus obtained 7-benzyloxy-4-(4-chloro-2-fluorophenoxy)-6-methoxyquinazoline (23.2 g); NMR Spectrum: ($DMSOd_6$) 3.98 (s, 3H), 5.34 (s, 2H), 7.42 (m, 9H), 7.69 (m, 1H), 8.55 (s, 1H).

A mixture of the material so obtained and trifluoroacetic acid (15 ml) was heated to reflux for 3 hours. The reaction mixture was allowed to cool, toluene was added and the mixture was evaporated. The residue was triturated under diethyl ether and then under acetone. The resultant precipitate was isolated and dried to give 4-(4-chloro-2-fluorophenoxy)-7-hydroxy-6-methoxyquinazoline trifluoroacetate salt (21.8 g) which was used without further purification.

Thereafter, a mixture of the trifluoroacetic acid salt of 4-(4-chloro-2-fluorophenoxy)-7-hydroxy-6-methoxyquinazoline (3.2 g), 3-(4-methylpiperazin-1-yl)propyl 4-toluenesulphonate (3.0 g), potassium carbonate (6.1 g) and DMF (60 ml) was stirred at 90°C for 5 hours. The resultant mixture was cooled to ambient temperature, poured into water (700 ml) and extracted with ethyl acetate (5 times). The combined extracts were washed in turn with water, a saturated aqueous sodium bicarbonate solution, water and brine. The ethyl acetate solution was dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using a 100: 8:1 mixture of methylene chloride, methanol and a concentrated aqueous ammonium hydroxide solution (0.880 g/ml) as eluent. The material so obtained was triturated under diethyl ether. There was thus obtained

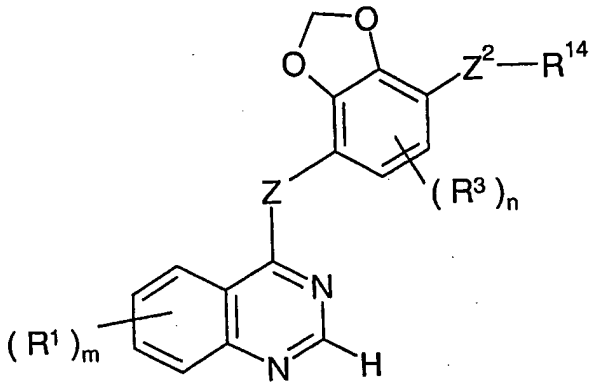
4-(4-chloro-2-fluorophenoxy)-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline (1.64 g); NMR Spectrum: ($DMSOd_6$) 1.95 (m, 2H), 2.14 (s, 3H), 2.35 (m, 8H), 2.44 (t, 2H), 3.96 (s, 3H), 4.22 (t, 2H), 7.38 (s, 1H), 7.4 (m, 1H), 7.54 (m, 2H), 7.68 (m, 1H), 8.55 (s, 1H).

After repetition of the previous reaction, a mixture of 4-(4-chloro-2-fluorophenoxy)-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline (2.6 g) and 2N aqueous hydrochloric acid solution (45 ml) was stirred and heated to 95°C for 2 hours. The mixture was cooled to ambient temperature and basified by the addition of solid sodium bicarbonate The mixture was evaporated and the residue was purified by column chromatography on silica using a 50: 8:1 mixture of methylene chloride, methanol and a concentrated aqueous ammonium hydroxide solution (0.880 g/ml) as eluent. There was thus obtained 6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]-3,4-dihydroquinazolin-4-one (1.8 g,); Mass Spectrum: $M+H^+$ 333.

After repetition of the previous reaction, a mixture of 6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]-3,4-dihydroquinazolin-4-one (2.15 g), thionyl chloride (25 ml) and DMF (0.18 ml) was stirred and heated to reflux for 2 hours. The thionyl chloride was evaporated under vacuum and the residue azeotroped twice with toluene. The residue was taken up in water, basified by the addition of a saturated aqueous sodium bicarbonate solution and extracted with methylene chloride (4 times). The combined extracts were washed in turn with water and brine and filtered through phase separating paper. The filtrate was evaporated under vacuum and the residue was purified by column chromatography on silica using a 100: 8:1 mixture of methylene chloride, methanol and a concentrated aqueous ammonium hydroxide solution (0.880 g/ml) as eluent. The solid so obtained was triturated under acetone, filtered and dried to give 4-chloro-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazoline (1.2 g); Mass Spectrum: $M+H^+$ 351.

CLAIMS

1. A quinazoline derivative of the Formula I



I

wherein each of Z, m, R^1, n, R^3, Z^2 and R^{14} have any of the meanings defined hereinbefore in the description.

2. A process for the preparation of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, according to claim 1 which comprises any one of the process variants (a) to (h) defined hereinbefore in the description.

3. A pharmaceutical composition which comprises a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, according to claim 1 in association with a pharmaceutically-acceptable diluent or carrier.

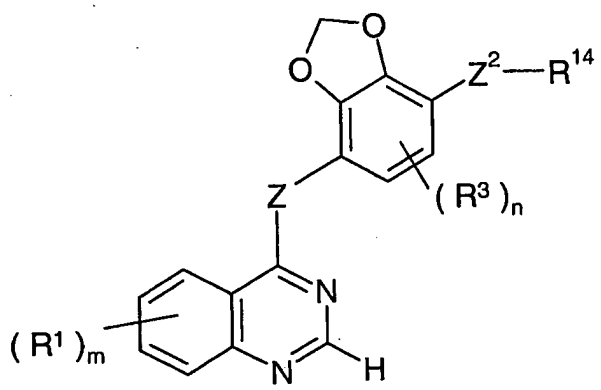
4. The use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, according to claim 1 in the manufacture of a medicament for use as an anti-invasive agent in the containment and/or treatment of solid tumour disease.

5. The use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, according to claim 1 in the manufacture of a medicament for use as an anti-proliferative agent in the containment and/or treatment of solid tumour disease.

A B S T R A C T

TITLE : QUINAZOLINE DERIVATIVES

The invention concerns quinazoline derivatives of Formula I



I

wherein each of Z, m, R^1, n, R^3, Z^2 and R^{14} have any of the meanings defined hereinbefore in the description; processes for their preparation, pharmaceutical compositions containing them and their use in the manufacture of a medicament for use as an anti-invasive or anti-proliferative agent in the containment and/or treatment of solid tumour disease.